

Thesis for the Degree of Master of Philosophy (Applied Epidemiology)

May Chiew

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**National Centre for Epidemiology and Population Health
Australian National University**

Field Placement

**National Centre for Immunisation Research and Surveillance of
Vaccine Preventable Diseases**

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**NCEPH supervisor
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A thesis submitted for the degree of Master of Philosophy of The Australian
National University

This thesis is my own original work and, where investigations are carried out jointly with others, it is clearly indicated in individual chapters what contribution I have made.

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31/7/2014



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Abstract

Vaccine Preventable Diseases– May Chiew BPharm, MPH

Vaccination is one of the most significant public health interventions in history. In this thesis, I present work conducted as an Master of Applied Epidemiology (MAE) Scholar whilst placed at the National Centre for Immunisation Research and Surveillance (NCIRS) in 2012–2013. During my placement, I was involved in examining the epidemiology of a number of vaccine preventable diseases and also adverse events following immunisation (AEFI). A key requirement of the MAE is the analysis of a public health dataset; of which I present two analyses. Firstly, the impact of the human papillomavirus vaccine on high grade cervical abnormalities (HGAs) in Australia using screening data; the analysis found a significant reduction in HGAs in females under 20 years post-vaccine compared to the pre-vaccine era, suggesting that the vaccine may have contributed to the decline in HGAs. Secondly, the epi-review on passive AEFI surveillance in children less than 18 years of age in 2000–2011 highlighted major events that occurred during this period. I also present two projects conducted as part of the measles outbreak in New South Wales (NSW) during 2012. The first was using a non-validated algorithm to identify an index case following four measles notifications that were linked by time and place to a paediatric hospital. The algorithm was unsuccessful in identifying an index case, however, may serve as a model that can be adapted and possibly validated for use in similar investigations in the future. The second was examining the epidemiology of healthcare transmissions during the outbreak. This study identified the importance of raising awareness of measles among clinicians during outbreaks and that measles control strategies may need a more targeted approach, particularly with limited resources. As part of my epidemiological study, I conducted an epi-review of measles in Australia. Since 1993, there was a considerable decline in measles notifications and hospitalisations; however, between 2000 and 2011, notifications have fluctuated with a notable increase in 2011. National notification data (2009–2011) were also used to estimate the reproduction number (R) for measles. The three methods to estimate R were below one for all years suggesting that measles elimination had been sustained in Australia. I also calculated a measles discard rate in NSW; an indicator of high quality surveillance. This study further supported sustained measles elimination achieving the minimum standard of more than 2 non-measles cases per 100,000 population suggesting that in NSW, endemic measles would be detected if wild virus was re-established. I also present another MAE requirement, evaluating the passive surveillance system for varicella-zoster virus

nationally, as part of the National Notifiable Disease Surveillance System. I found that the sensitivity of the system in detecting the incidence of disease was poor; however, it was sensitive in detecting disease trends in when compared to other data sources. Additionally, more consistency in reporting by jurisdictions is necessary to improve the validity of the data. This thesis provides documentation of my MAE activities at NCIRS and includes how these activities have contributed to public health in Australia.

About this thesis

Four chapters in my MAE thesis include the four MAE projects: data analysis; epidemiological study; outbreak investigation and; evaluation of a surveillance system.

Data analysis is separated into two chapters (Chapters 2 and 3), as I analysed two public health datasets for two very different conditions (adverse events following immunisation and high grade cervical abnormalities). Chapter 4 includes both the epidemiological study and outbreak investigations as these projects belong under the broader subject of measles. Lastly, Chapter 5 contains the evaluation of a surveillance system.

Each chapter includes a separate table of contents and lists of figures, tables, abbreviations and acronyms and references, as each chapter is independent of each other, and is hence easier to refer to.

On 18 September 2013, the machinery of Government changes resulted in the name change of the Department of Health and Ageing to the Department of Health. Please note that the former name is used throughout this thesis.

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Chapter 1

Introduction

Acronyms and Abbreviations

| | |
|-------|--|
| ATAGI | Australian Technical Advisory Group on Immunisation |
| CDI | Communicable Diseases Intelligence |
| CDNA | Communicable Diseases Network of Australia |
| DoHA | Department of Health and Ageing |
| HGA | High Grade Cervical Abnormalities |
| HPV | Human Papillomavirus |
| MAE | Master of Philosophy (Applied Epidemiology) |
| NCEPH | National Centre for Epidemiology and Population Health |
| NCIRS | National Centre for Immunisation Research and Surveillance |
| NIP | National Immunisation Program |
| NSW | New South Wales |
| PAEDS | Paediatric Active Enhanced Disease Surveillance |
| PhD | Doctor of Philosophy |
| TGA | Therapeutic Goods Administration |
| WPRO | Western Pacific Regional Office |
| VPD | Vaccine Preventable Diseases |

1.1 A field placement at the National Centre for Immunisation Research and Surveillance

My first introduction to the Master of Philosophy (Applied Epidemiology) (MAE) program was an advertisement that I received from the Australian Epidemiological Association. I had been contemplating whether to embark on a Doctor of Philosophy (PhD) in cancer epidemiology but was at a crossroads. I had always had an interest in infectious diseases and wanted more 'hands-on' experience in epidemiology as opposed to focusing solely on research. Fortuitously, I noticed the advertisement and took it as a sign to apply.

National Centre for Immunisation Research and Surveillance

The National Centre for Immunisation Research and Surveillance of Vaccine Preventable Disease (NCIRS) was established by the Commonwealth Department of Health and Ageing in 1997 as part of the Immunise Australia: Seven Point Plan.¹ One initiative of the Immunise Australia program was to improve surveillance and reporting mechanisms for immunisation coverage, incidence of vaccine preventable diseases (VPDs) and outbreaks of VPDs.

NCIRS envisages to reduce the incidence of VPDs and to increase vaccine coverage in children and adults. And endeavours to be the leading national source of evidence for immunisation policy and practice whilst upholding scientific independence and high credibility. NCIRS also aims to be the foremost immunisation related information provider for health care professionals.

NCIRS manages and conducts epidemiological and serological research and analysis of VPDs and on immunisation which assists state and Commonwealth health departments in informing immunisation related policy. NCIRS' mission is "to promote the optimum control of vaccine preventable diseases in Australia through research, surveillance and evaluation of scientific evidence." Key activities of NCIRS includes surveillance, policy support, disease modelling, adverse events following immunisation (AEFI), the Paediatric Active Enhanced Disease Surveillance (PAEDS), vaccine program evaluation, clinical research, individual and social research and the provision of health care professional support.

1.2 Summary of public health experiences and impact

During my time at NCIRS, I was involved in a number of projects that provided me with a broad range of public health experiences, of which had significant public health impact.

Firstly, I was involved in assessing the impact of the human papillomavirus (HPV) vaccine using screening data, which to my knowledge, was the first a detailed analysis has been conducted at a national level, globally. This was of particular interest to the Communicable Diseases Network of Australia (CDNA) HPV working party. The results of the project will also be part of the overall evaluation of the HPV vaccination program. The results of this project identified a reduction in high grade abnormality (HGA) rates in females eligible for HPV vaccine under the National Immunisation Program (NIP). It also explored the strengths and limitations of using screening data to examine the impact of the vaccine. A written report will be provided to the Department of Health and Ageing (DoHA), and there is a plan to develop a manuscript to submit to a peer-reviewed journal.

Additionally, I conducted data analysis on AEFI reports in children < 18 years between 2000 and 2011. Following some major AEFI events in Australia during this period, the project reviewed the landscape of AEFI in the country, including the strengths and limitations of the passive surveillance of AEFI and how reporting has evolved over time. A review had not been conducted in Australia beforehand for this particular age group. A report will be submitted to the Therapeutic Goods Administration (TGA) and a manuscript submitted to the Communicable Diseases Intelligence (CDI) journal.

During 2012, I was involved in investigating two outbreaks which enabled me to fulfil my outbreak requirements. The first was a *Staphylococcal aureus* foodborne outbreak at an elite sporting event (**Appendix A2**). This outbreak highlighted to me the challenges associated with investigating an outbreak with limited resources and in a timely manner. Also, it enabled me to understand that often, a source and vehicle for contamination cannot be identified and obtaining food samples or specimens from individuals is difficult. It also identified the important role that laboratories play during outbreaks. Co-leading this investigation equipped me with experience in developing a food exposure questionnaire, interviewing individuals and the analysis and interpretation of data collected. A report was developed and provided to the NSW Ministry of Health. There is a lack of reporting of *Staphylococcal aureus* foodborne

outbreaks in the literature and this outbreak added new knowledge to the understanding of *Staphylococcal aureus* outbreaks through a manuscript that I co-authored with my fellow MAE published in CDI. The second outbreak investigation I was involved in was the 2012 NSW measles outbreak, with a specific focus on health-care transmissions of measles. The measles outbreak provided me with an understanding of the operational response to an extremely infectious disease. I was able to gain experience in contact tracing, participating in post-exposure prophylaxis clinics, visiting emergency departments where transmissions occurred and working as surge staff in a number of local health districts and the NSW Ministry of Health. A manuscript was developed to highlight the importance of healthcare transmissions in an era where measles elimination exists and aims to raise awareness among clinicians in the suspicion of measles during times or measles outbreaks. A report on healthcare transmissions of measles during this outbreak was provided to the NSW Ministry of Health, and the results were also provided to the Measles Elimination working party. A manuscript is also planned for submission to a peer-reviewed journal.

My epidemiological study chapter is comprised of three inter-related projects related to measles elimination in Australia and also includes the public health investigations on measles. I was fortunate not only to be involved in these three projects, but for their results to be used as evidence in assessing Australia's measles elimination status to be reviewed by the Regional Measles Verification Committee for the Western Pacific Region. I gained a lot of experience in cleaning and analysing data and also understanding the caveats in notification and laboratory data. Conducting an epi-review on measles notifications allowed me to familiarise myself with notification data and understand the national picture of measles in the country and the role of the vaccine program on disease incidence. I also used notification data in a modelling project which estimated the reproduction number (R) for measles. One aspect that I was hoping to understand more of before embarking on the MAE program was infectious disease modelling; and being involved in estimating R was a fantastic opportunity to grasp some understanding of modelling but also acknowledging the limitations associated with modelling. Furthermore, calculating the measles discard rate allowed me to gain an understanding on the types of testing that is conducted for measles. The measles R project has been accepted at the Bulletin of the World Health Organization. The measles epi-review will be submitted to CDI and the measles discard rate project will contribute to a national measles discard rate paper that is being developed by members of the National Measles Elimination Working Group. The results of this

chapter is of significant public health impact as it adds to the argument of whether measles elimination has been sustained in Australia and will contribute to determining whether Australia can formally verify measles elimination in the country given the Region's target of measles elimination in 2012.

I also evaluated the national notification of varicella zoster viruses (chickenpox shingles and unspecified). This project provided me with the opportunity to liaise with jurisdictional and Commonwealth Stakeholders, develop a questionnaire, collaborate with multiple researchers using other data sources and examine multiple lines of evidence to generate key recommendations. A range of recommendations aim to improve the notification system, particularly the utility of it to monitor the impact of the vaccination program. This project is of particular interest to the National Surveillance Committee, CDNA Varicella Working Group and CDNA Herpes Zoster Working Group who are responsible in advising and implementing change to the surveillance system. A report will be disseminated to Jurisdictional and Commonwealth stakeholders as well as the working groups abovementioned. There are plans to also develop a manuscript to submit to a peer-review journal.

Lastly, I participated in the Field Epidemiology Training Program Fellowship as a Rumour Surveillance Officer at the Western Pacific Regional Office of the World Health Organization (WHO) for five weeks in July and August 2013. I was responsible for collecting public health events through rumour and official channels; conducting rapid risk assessments on public health events; presenting public health events to colleagues working in the Division of Health Security and Emergencies; preparing reports; and liaising with surveillance staff from Country Offices within the region. Undertaking the fellowship enabled me to experience working in a multilateral organization for the first time. I learnt many things during my time there. Firstly, I learnt how to scan rumour channels for potential public health events of importance, systematically followed a rapid risk assessment algorithm to determine what actions were required, garnered more knowledge on the International Health Regulations (2005) and Asia Pacific Strategy for Emerging Diseases (2010) and the role that the World Health Organization plays and lastly, I learnt about many infectious diseases affecting the region that I was unfamiliar with.

1.3 Summary of core activities to meet MAE requirements

Analyse a public health dataset

- The impact of human papillomavirus vaccine on high grade cervical abnormalities in females < 20 years in Australia
- A twelve-year review of adverse events following immunisation in children < 18 years in Australia

Outbreak investigations

- Identifying the source case of measles in a paediatric emergency department in Sydney
- Healthcare acquired measles during the 2012 measles outbreak in NSW

Epidemiological study

- A review of measles epidemiology in Australia; 2000—2011
- Estimating the measles reproduction number using notification data
- Calculating the measles discard rate in NSW

Evaluation of a surveillance system

- Evaluation of the national varicella surveillance system in Australia

Scientific manuscript for a peer-reviewed journal

- Chiew M, Gidding HF, Dey A, Wood J, Martin N, Davis N, McIntyre P (2013) Evaluation of the measles reproduction number (R) as a practical means to track maintenance of measles elimination using routine notification data—the Australian experience. Bulletin of the WHO (accepted).

Report for a public health bulletin

- Chiew M, Dey A, Martin N, McIntyre P (2013). The epidemiology of measles in Australia; 2000—2011. CDI (late draft to be submitted)

Report to a lay audience

- Chiew M (2013) Immunisation and changes in benefits. WebChild blog
<http://www.webchild.com.au/health/health-and-wellbeing/immunisation-and-changes-in-benefits>

Conference presentations

- Chiew M, Gidding HF, Dey A, Davis S, McIntyre P (2012) Transmission of measles in an era of elimination in Australia; TEPHINET 7th global conference, Amman, Jordan.

I also gave several other oral presentations during the MAE program:

- NCIRS Journal Club – 29 November 2012 and 9 September 2013
- NCIRS Academic Meeting – 29 October 2013
- Infectious Disease Meeting at the Children's Hospital Westmead – 31 October 2012
- Western Pacific Regional Office, Division of Health Security and Emergencies meeting–30 August 2013

Lessons from the field

- The verification of measles elimination in the Western Pacific: Has Country X achieved elimination?

Teaching

- Pre-CDC Conference workshop: Introduction to Epi Info™
- MAE 2013 cohort exercises: Outbreak investigation intensives course block

Coursework

I completed the required MAE courses below:

- POPH8316 Outbreak investigation
- POPH8317 Public health surveillance
- POPH 8312 Research project in applied epidemiology
- POPH 8313 Analysis of public health data
- POPH 8315 Methods in applied epidemiology

Course block residential

- I attended the MAE residential blocks during March 2012, August 2012 and March 2013.

Other workplace activities

- Member of the National Measles Elimination Working Group Party
- Five-week Field Epidemiology Training Program Fellowship at the Western Pacific Regional Office in Manila, Philippines

- Co-led an outbreak investigation at an elite sporting events in 2012 in western Sydney

Table 1: Summary of MAE course requirements included in the bound volume

| Course requirement | Chapter 1 Introduction | Chapter 2: Human Papillomavirus Vaccine Impact Analysis | Chapter 3: Analysis of passive surveillance of adverse events following immunisation | Chapter 4: Measles-on the path to elimination | Chapter 5: Evaluation of the passive surveillance of varicella infection in Australia | Chapter 6: Teaching |
|---|---------------------------|--|---|--|--|------------------------|
| Analyse a public health dataset | | ✓ | ✓ | | | |
| Evaluation or implementation of a public health surveillance system | | | | | ✓ | |
| Conduct a field investigation | | | | ✓ | | |
| Conduct and interpret an epidemiological study | | | | ✓ | | |
| Literature review | | ✓ | ✓ | ✓ | ✓ | |
| Scientific manuscript for a peer-reviewed journal | | ✓ | ✓ | ✓ | | |
| Public health bulletin | | | | ✓ | | |
| Give an oral presentation | | | | ✓ | | |
| Report to a lay audience | ✓ | | | | | |
| Lesson from the field and teaching | | | | | | ✓ |

References

1. Department of Health and Ageing. Immunise Australia: Seven Point Plan. [updated 15 Jan 2013; cited 2013 20 Oct]; Available from: <http://www.health.gov.au/internet/immunise/publishing.nsf/Content/history-of-ia-prog>

Appendix A

A1.1 Report to a lay audience



Immunisation And Changes In Benefits

Written by May Chiew | 24 July 2013



May Chiew looks into the new immunisation requirements parents must meet to be eligible for the Family Tax Benefit Part A supplement.

The Australian Government provides a number of payments to assist families in the cost of raising children, including the Family Tax Benefit Part A supplement. To be eligible for this benefit, children need to be 'fully immunised' against certain diseases by the end of the financial years in which they turn one, two and five years of age.

What Are The Changes?

As of 1 July this year, three new diseases were added to the list of diseases children must be vaccinated against to receive the Family Tax Benefit Part A supplement. These are varicella (chickenpox), meningococcal C and pneumococcal disease. Also, the age at which children need to have their second dose of measles, mumps and rubella (MMR) vaccine has been brought forward from four years to 18 months.

To ensure they have received the required vaccines at the right time, a child's immunisation status will be assessed after parents lodge their tax return, by checking the Australian Childhood Immunisation Register – the register that records immunisations given to children under seven years of age.

What Do These Changes Mean?

Under the National Immunisation Program (NIP), three doses of vaccine against pneumococcal disease are recommended by six months of age. One dose of meningococcal C- containing vaccine and the first dose of MMR are recommended at one year of age. The vaccine against varicella (chickenpox) and the second dose of MMR are recommended at 18 months of age, and will now be given as a combination vaccine: the measles, mumps, rubella and varicella (chickenpox) vaccine (MMRV).

If a child has already received the 18-month varicella (chickenpox) vaccine but not the 4-year MMR vaccine, the MMR vaccine will be given at 4 years of age.

Why The Changes?

These changes aim to increase the number of children who receive their recommended vaccines on time. Having the majority of children vaccinated means more children will be protected against these diseases, and that the amount of immunity in the community is high enough to protect those who can't be vaccinated because they are too young or because of medical reasons. Having high immunity in the community is also important to prevent disease outbreaks.

Moving the second dose of MMR-containing vaccine from four years to 18 months of age will protect children earlier against these three diseases. Also, the combination vaccine, MMRV, means children will be protected against the four diseases, with one less needle given.

Will These Changes Cost Anything?

Like all other vaccinations linked to family-assistance payments, the vaccinations against these three additional diseases are provided free of charge under the NIP.

Are There Any Exemptions?

Parents can be given an exemption from meeting the Family Tax Benefit Part A supplement immunisation requirements if their child is not 'fully immunised' due to medical reasons, their parents' personal or religious beliefs, or if their child is on a recognised catch-up plan. A form approving this exemption needs to be certified by a GP or an immunisation provider.

Where Can I Get More Information?

Further information can be found on the Immunise Australia website at:
<http://immunise.health.gov.au/internet/immunise/publishing.nsf/Content/home>

A full list of diseases a child needs to be vaccinated against can be found at:
<http://www.humanservices.gov.au/customer/subjects/immunising-your-children>

May Chiew is a Master of Applied Epidemiology Scholar for at the National Centre for Immunisation Research and Surveillance in Sydney.

AN OUTBREAK OF STAPHYLOCOCCAL FOOD POISONING IN A COMMERCIAL CATERED BUFFET

Alexis Rillsbury, May Chiew, John Bates, Vicky Sheppeard

Abstract

Staphylococcal food poisoning is a common cause of foodborne illness. In Australia, since 2000, approximately 30% of foodborne *Staphylococcus aureus* outbreaks reported to OzFoodNet have been associated with foods prepared by commercial caterers. We conducted a retrospective cohort analysis of an outbreak of gastrointestinal illness among participants of an elite sporting event during which 22 individuals became ill after eating a commercially catered buffet dinner in June 2012. All recalled eating fried rice which had been intended for lunch service earlier that day and 20 of the 22 reported eating chicken stir-fry. Though no food samples were available for analysis, laboratory analysis conducted on four faecal specimens resulted in *S. aureus* being cultured from one specimen and *S. aureus* enterotoxin detected in another. The known epidemiology of staphylococcal food poisoning suggests a food contaminated by an infected food handler which was subject to temperature abuse may have caused the outbreak. As *S. aureus* foodborne outbreaks are often underreported, this investigation is a valuable contribution to the evidence-base and understanding of foodborne illness due to *S. aureus* and staphylococcal enterotoxin.

Keywords: *Staphylococcus aureus*, enterotoxins, outbreak, foodborne, rice, chicken

Introduction

Staphylococcal food poisoning (SFP) is a common cause of foodborne illness worldwide.¹⁻³ SFP occurs following ingestion of staphylococcal enterotoxins which are heat resistant and are produced in food following contamination by staphylococci, typically *Staphylococcus aureus*. Foods including sliced meat, meat products, salads, pastries, custards, raw milk and cheese products present a particular contamination risk.¹ Such a large population of staphylococci is indicative of unhygienic food handling procedures and temperature abuse over a period of time to allow for bacterial growth.⁴

In Australia, little published information exists describing past SFP outbreaks. OzFoodNet, however, collects information on all reported foodborne illness outbreaks. Between January 2000 and March 2012, OzFoodNet recorded 14 *S. aureus* outbreaks affecting 429 people (25 hospitalised; 1 death). In

just under a third of these outbreaks, meals containing chicken were implicated. Twenty-nine per cent of these outbreaks were associated with food prepared by a commercial caterer (OzFoodNet Outbreak Register, June 2012. Unpublished data).

The outbreak

On 2 June 2012, 22 individuals who had participated in an elite sporting event in Sydney experienced gastrointestinal symptoms after eating a buffet dinner served by the commercial catering company servicing the event. The day of the outbreak was the final day of the two week event and reportedly less busy at dinner time than previous meals. The 22 individuals were part of a larger cohort of up to 40 people who queued for dinner service earlier than the other 500 attendees due to the timing of their responsibilities at the event. Within hours of eating, all 22 fell ill with symptoms including vomiting, diarrhoea and abdominal cramping. Six people were transported to hospital. The event organiser reported that only the early dining group was affected.

This report summarises the epidemiological and microbiological investigations into the cause of the outbreak.

Methods

Epidemiological investigation

As this epidemiological investigation was conducted as part of the required public health response to a reported outbreak, it was not necessary to obtain ethical approval.

In order to develop hypotheses regarding the cause of the outbreak, preliminary interviews were conducted by telephone with several of the cases who attended the emergency department (ED) due to the severity of their symptoms. We drafted a food exposure questionnaire based on information from these interviews and information from a copy of the menu provided by the caterers. The questionnaire sought basic demographic details, food exposures (lunch and dinner), symptom description and duration, and illness history. Individuals were also

asked whether they were aware of anyone who had been ill with gastrointestinal symptoms prior to or following the outbreak.

A case was defined as anyone who ate the catered buffet dinner on 2 June 2012 at the early time (16:00 to 17:30) and experienced vomiting and/or diarrhoea and abdominal cramping commencing between 17:45 and 21:15. A confirmed case was someone meeting the case definition with *S. aureus* or *S. aureus* toxin detected in a stool specimen.

The names of the cases as well as others who were thought to have dined early were provided by the event organisers, Ambulance Service NSW, and other interviewed attendees. Based on the knowledge gleaned from these interviews, we conducted a retrospective cohort investigation to identify risk factors for developing illness. Interview data were collated and attack rates and risk ratios were calculated for specific food exposures. Analysis was conducted using SAS[®] software (version 9.3).

Microbiological and environmental investigations

No food samples were available for testing. Faecal specimens were collected from 5 of the individuals who attended the ED. Initial testing for *Clostridium difficile*, *Salmonella*, *Shigella* and *Campylobacter* species and norovirus was conducted by the hospital laboratory.

Four specimens were available to be sent to Queensland Health Forensic and Scientific Services laboratory where they were cultured for a full range of enteric pathogens (including *Salmonella*, *Shigella* and *Campylobacter* species) and toxin-mediated foodborne illness causing bacteria (*S. aureus* and *Bacillus cereus*). Samples were cultured on Baird Parker Agar for two days at 37°C for *S. aureus* and Phenol-Red Egg Yolk Polymyxin Agar for *B. cereus*. Three faecal samples were tested for staphylococcal enterotoxin using the Tecra enzyme-linked immunosorbent assay (TECRA). A site inspection was conducted by NSW Food Authority and is the subject of a separate internal report.

Results

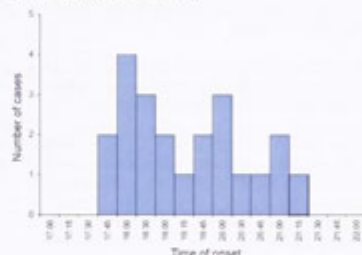
Epidemiological results

A total of 36 persons who ate an early dinner served by the caterer were interviewed, with the majority interviewed 2 to 3 days after the incident. The median age of people interviewed was 40 years (range 12 to 72 years); 78% were female. Among the 36 persons interviewed, 22 (61%) were identified as cases, including two persons with laboratory-confirmed illnesses.

Of the 22 cases, 18 (82%) were female, ranging from 12 to 69 years old (median 34 years). Of those who did not fall ill, 10 (71%) were female, ranging from 21 to 72 years old (median 46 years).

Dinner times reported by cases ranged from 16:00 to 17:30. The epidemic curve illustrates the time distribution of symptom onsets among cases ranging over a 4 hour period on 2 June (Figure 1). Incubation periods ranged from 1 hour to 4.75 hours (average 2.5 hours). Illness typically began with the sudden onset of vomiting, followed by a period of concurrent vomiting and diarrhoea, with a median duration of 4 hours (range 2 to 13 hours). Of the 22 cases, 21 experienced vomiting (96%); 17 had diarrhoea (77%) and 10 reported abdominal cramping (46%). Six people (27%) were transported to a local ED. No interviewees were aware of others with symptom onset of gastrointestinal illness prior to or following the outbreak.

Figure 1: Number of cases of gastrointestinal illness after the catered dinner on 2 June 2012, by time of onset (n=22)



A number of food items were served during lunch and dinner. A selection of bread, cold meats (ham, chicken, turkey and silverside), salad and fried rice were available at lunch. Green salad, coleslaw, meatballs, cannelloni, boiled rice, fried rice, chicken stir-fry, bread rolls, jelly and yoghurt were served for dinner. Fried rice intended for lunch service on the day of the outbreak was reportedly served to the early diners because the boiled rice for dinner service was not ready in time.

All interviewees had eaten dinner early at the catered buffet while only 14 (39%) ate lunch there. Ninety-one per cent of cases ate both chicken stir-fry and fried rice at dinner with attack rates and rate differences of 74% for chicken stir-fry and 71% for fried rice (Table 1). The risk ratios for both dishes were undefined. Similarly, we were unable to conduct further analysis using stratification. Therefore it was not possible to identify an association with either chicken stir-fry or fried rice.

Table 1: Relative risks and attack rates for food items consumed by the cohort

| Salad | 5 | 7 | 71 | 17 | 29 | 59 | 1.22 (0.70-2.13) | 0.68 |
|------------------|-----|----|-----|----|----|----|------------------|--------|
| Coleslaw | 2 | 2 | 100 | 20 | 34 | 59 | 1.70 (1.28-2.25) | 0.51 |
| Meatballs | 15 | 24 | 63 | 7 | 12 | 58 | 1.07 (0.61-1.89) | 1.00 |
| Cannelloni | 14 | 25 | 56 | 8 | 11 | 73 | 0.77 (0.47-1.27) | 0.47 |
| Fried rice | 22 | 31 | 71 | 0 | 5 | 0 | undefined | 0.005 |
| Chicken stir-fry | 20* | 27 | 74 | 0 | 7 | 0 | undefined | 0.0006 |
| Yoghurt | 5 | 8 | 63 | 17 | 28 | 61 | 1.03 (0.56-1.90) | 1.00 |
| Jelly | 8† | 13 | 62 | 13 | 22 | 59 | 1.04 (0.60-1.81) | 1.00 |
| Bread roll | 11‡ | 17 | 65 | 7 | 14 | 50 | 1.29 (0.69-2.43) | 0.48 |

* 2 missing

† 1 missing

‡ 5 missing

Microbiological and environmental results

Initial screening results for all five specimens were negative for norovirus, *C. difficile*, *Salmonella*, *Shigella* and *Campylobacter* species.

Queensland Health Forensic and Scientific Services laboratory cultured *S. aureus* in one specimen. Another specimen tested positive for *S. aureus* enterotoxin.

Though no food samples remained for laboratory testing, the catering company confirmed that food handling policies were in place to prevent contamination as well as time and temperature abuse. No evidence of time and temperature abuse was observed during the site inspection. The catering company also reported that no staff members were known to be suffering from gastrointestinal illness during the sporting event.

Discussion

S. aureus is one of the most common pathogens in humans, estimated to colonise approximately 25% of healthy adults.² Multiple pathogenic strains produce enterotoxins which, when ingested, can cause gastroenteritis.⁸ In Australia, *S. aureus* intoxication accounted for 1% of all suspected and confirmed foodborne outbreaks reported to OzFoodNet between January 2000 and March 2012. Meals including chicken, beef, seafood, and lamb, as well as pasta salad and rice dishes have all been implicated as source of infection in these *S. aureus* enterotoxin outbreaks (OzFoodNet Outbreak Register, June 2012. Unpublished data).

Our findings suggested that chicken stir fry and/or fried rice were the food vehicles responsible for illness. Although it was not possible to determine risk ratios for fried rice and chicken stir-fry, the attack rates and rate

differences calculated support this conclusion. It was not possible to consider these exposures independently as all cases who were able to recollect reported eating both food items.

SFP outbreaks result from contamination of food with *S. aureus* from food handlers either through skin infection on uncovered hands or arms, or via coughing or sneezing over food that is not subjected to further cooking. Current industry guidelines require food handlers to ensure their bodies, and anything from their bodies or clothing, do not contaminate food or food preparation areas.⁹ For the bacteria to grow to sufficient numbers, the contaminated food must be left in temperature conditions where the bacteria are able to proliferate. *S. aureus* produces pre-formed toxins that have an emetic and diarrheal effect.¹

In this investigation, there was no evidence of temperature abuse and we were unable to definitively identify a cause of the outbreak. The environmental investigation revealed no food safety breaches, and the absence of food samples made it impossible to identify the food vehicle responsible for the outbreak. The only apparent difference in foods served to the early diners was the fried rice which had been intended for lunch service.

To prevent toxin-based outbreaks, it is important that commercial food providers adhere to strict temperature protocols and ensure good food handling practices. Management and staff need to be alert to the presence of infected skin lesions or discharges from nasal passages, ears or eyes in food handlers. Appropriate measures should be taken to ensure that no ill individuals can contaminate food or food contact surfaces.¹⁰

Investigation of toxin-mediated foodborne illness is particularly problematic due to short onset times and duration of symptoms. Furthermore, as *S. aureus* is not a notifiable disease outbreaks often go undetected. This outbreak was only likely to have been reported due to the nature of the sporting event and the large number of individuals affected.

Limitations

This investigation was limited in several ways. Though interviews were conducted as soon as possible following the outbreak, a number of individuals had difficulty remembering all foods consumed. A high proportion of individuals who dined early strongly believed that the fried rice intended for lunch was the infection source. Moreover, participants had extensively discussed the outbreak and theories on its cause, predominantly through social media, potentially introducing bias to the investigation.

The microbiological investigation was also impacted by limitations. Firstly, initial analyses of faecal specimens were restricted to in-house PCR assays and not cultured as per the NSW Health outbreak protocol which specifies that all faecal specimens related to potential outbreaks undergo routine enteric culture. Nevertheless, *S. aureus* is unlikely to be grown using routine culture, and the delay which ensued from the need to transport samples to Queensland for toxin testing would have decreased the yield when appropriately cultured there. Given the time delay between onset and receipt of the samples and the variable storage temperatures of the samples during that time, it is unsurprising that only 1 positive result was returned. This underlines the importance of good communication between public health investigators and laboratories so that specimens are tested according to the clinical and epidemiological picture. Additionally, vomitus specimens would have been preferable for analysis as staphylococcal enterotoxin is cleared from the gut quite quickly. Unfortunately, no samples of vomitus were collected as this is not a routine practice in EDs and vomiting had resolved before the public health investigation commenced.

Conclusion

Information obtained from case interviews and the results of microbiological testing of human specimens support a conclusion that enterotoxigenic *S. aureus* bacteria were responsible for this outbreak. We were unable to definitively identify a food vehicle in this outbreak. *S. aureus* associated outbreak reports are rarely published in Australia despite being such a common cause of

foodborne illness worldwide. This investigation improves our understanding of the epidemiology of foodborne *S. aureus* outbreaks in Australia.

Acknowledgements

We are grateful to NSW Food Authority for conducting the environmental investigation; OzFoodNet for providing data on reported Australian gastrointestinal outbreaks due to *S. aureus* infection from the OzFoodNet Outbreak Register; Drs Martyn Kirk and Stephanie Davis of the ANU Master of Philosophy (Applied Epidemiology) program for guidance; NCIRS for providing us the time and resources to conduct the investigation; Jennie Musto for comments on the report; and the staff at Nepean Blue Mountains and Western Sydney Public Health Unit for support and assistance. We gratefully acknowledge the staff of Public Health Microbiology, Queensland Health Forensic & Scientific Services, who performed the technical work on these faecal samples.

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References

1. Centers for Disease Control and Prevention (CDC). National Center for Emerging and Zoonotic Infectious Diseases (NCEZID), Division of Foodborne, Waterborne, and Environmental Diseases (DFWED). Staphylococcal food poisoning 2010 [updated June 7 2010]. Available from: <http://www.cdc.gov/ncezid/divisions/dfwed/diseases/staphylococcal/>
2. Heymann DL. Control of communicable diseases manual. American Public Health Association; 2008.

3. Hennekinne JA, De Buyser ML, Dragacci S. Staphylococcus aureus and its food poisoning toxins: characterization and outbreak investigation. *FEMS Microbiology Reviews*. 2012;36(4):815-36.
4. Ostyn A, De Buyser M, Guillier F, Groult J, Felix B, Salah S, et al. First evidence of a food poisoning outbreak due to staphylococcal enterotoxin type E, France, 2009. *Euro Surveill*. 2010;15(13):1-4.
5. Jelastopulu E, Venieri D, Komninou G, Kolokotronis T, Constantinidis T, Bantias C. Outbreak of acute gastroenteritis in an air force base in Western Greece. *BMC public health*. 2006;6(1):254.
6. Asao T, Kumeda Y, Kawai T, Shibata T, Oda H, Haruki K, et al. An extensive outbreak of staphylococcal food poisoning due to low-fat milk in Japan: estimation of enterotoxin A in the incriminated milk and powdered skim milk. *Epidemiology and infection*. 2003;130(1):33-40.
7. Da Carmo LS, Cummings C, Linardi VR, Dias RS, De Souza JM, De Sena MJ, et al. A case study of a massive staphylococcal food poisoning incident. *Foodborne Pathogens & Disease*. 2004;1(4):241-6.
8. Lowy FD. Staphylococcal Infections. Harrison's Principles of Internal Medicine. 18th ed. New York: McGraw-Hill; 2012.
9. NSW Food Authority. Health and hygiene for food handlers. 2012 [updated 27 May 2011; cited 2012 October 31]; Available from: <http://www.foodauthority.nsw.gov.au/industry/food-business-issues/health-and-hygiene-for-food-handlers/>
10. Food Standards Australia New Zealand. Food Safety Standards - Health and hygiene: Responsibilities of food businesses: Chapter 3 (Australia only) Australia New Zealand Food Standards Code. 2012 [updated July 10 2012; cited 2012 July 23]; Available from: <http://www.foodstandards.gov.au/scienceandeducation/factsheets/foodsafetyfactsheets/healthandhygieneresp102.cfm>.



The impact of Human Papillomavirus Virus (HPV) vaccine on high grade cervical abnormalities in Australia

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Chapter 2

The impact of Human Papillomavirus Virus (HPV) vaccine on high grade cervical abnormalities in Australia

Late draft to be submitted to a peer-reviewed publication

Chiew M, Dey A, Liu B, Brotherton J, Bradley M, Willis J, McIntyre P

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Abbreviations & Acronyms

| | |
|--------------|--|
| ABS | Australian Bureau of Statistics |
| ACT | Australian Capital Territory |
| AIHW | Australian Institute of Health and Welfare |
| ANU | Australian National University |
| CIN2+ | Cervical Intraepithelial Neoplasia of Grade 2 |
| CIN3+ | Cervical Intraepithelial Neoplasia of Grade 3 |
| DoHA | Department of Health and Ageing |
| HGA | High Grade Cervical Abnormalities |
| HPV | Human Papillomavirus |
| IARC | International Agency for the Research on Cancer |
| MAE | Master of Philosophy (Applied Epidemiology) |
| NCIRS | National Centre for Immunisation Research and Surveillance |
| NCSP | National Cervical Screening Program |
| NHMD | National Hospital Morbidity Database |
| NHPVR | National Human Papillomavirus Vaccination Program Register |
| NHVP | National HPV Vaccination Program |
| NIP | National Immunisation Program |
| NSW | New South Wales |
| NT | Northern Territory |
| QLD | Queensland |
| RR | Rate Ratio |
| SA | South Australia |
| TAS | Tasmania |
| UNSW | University of New South Wales |
| VIC | Victoria |
| WA | Western Australia |

Abstract

Introduction:

In 2007, Australia implemented a national human papillomavirus (HPV) vaccine program, the first country in the world to fund the vaccine through a national program. HPV-related cervical abnormalities, are a precursor to the development of cervical cancer and through data from the well-established National Cervical Screening Program, it was timely to examine the impact of the HPV vaccine program on the detection of cervical abnormalities.

Methods:

Data on screening participation and high grade cervical abnormalities (HGAs) were obtained from cervical cancer screening reports published by the Australian Institute of Health and Welfare (2004–2011). Corresponding population estimates for these years were obtained from the Australian Bureau of Statistics. Absolute rates (RR) of HGAs detected and rate ratios comparing post-vaccine and pre-vaccine rates were calculated

Results:

Between 2004 and 2011, cervical screening rates for all age groups declined. The rate of HGAs post vaccine (2008–2011) was found to be significantly lower than during the pre-vaccine (2004–2007) with a 34% decline (95% CI: 30%–37%) in females <20 years. Reductions were observed even when accounting for decline in screening participation among <20 years.

Conclusion:

Our results provide evidence that the rate of HGA among females <20 years, who were targeted for the HPV vaccine has significantly declined following the introduction of the HPV vaccine program. Although inference between the vaccine and HGA detection cannot be asserted due to the nature of the study, our preliminary results suggest that HPV vaccine is effective in reducing the incidence of HGAs. Further prospective cohort studies are required to provide evidence-base for the association between the two.

Prologue

My role

Prior to starting the Master of Philosophy (Applied Epidemiology) (MAE), I met with Drs Aditi Dey, Helen Quinn and Robert Menzies, all senior researchers at National Centre for Immunisation Research and Surveillance (NCIRS). NCIRS are involved in policy and adverse event research on Human Papillomavirus (HPV) vaccines and at that time were in discussions with the Department of Health and Ageing (DoHA) to evaluate the National HPV Vaccination Program (NHVP) with a number of other collaborators. They wanted to gauge my interest in working on HPV vaccine related projects, of which I was extremely interested given my work at Cancer Council NSW on cancer screening.

Towards the end of my first year (2012) as an MAE scholar, Aditi and I commenced a project looking at the impact of HPV vaccine on the rate of high grade cervical abnormalities (HGA) in females targeted for the vaccine. I was the primary investigator in this study, which was conducted as part of the evaluation of the NHVP. My role included developing a project proposal, reviewing the literature, conducting data analysis and drafting a manuscript for the project, which is included in this chapter.

This manuscript was very much a partnership, as I worked closely with Aditi, who provided me with advice and guidance during all stages of the project. Aditi's role included reviewing the project plan, providing advice during data analysis and providing feedback on the draft report. Professor Peter McIntyre, Director of NCIRS, Dr Julia Brotherton (Victorian Cervical Cytology Service), Dr Dorota Gertig (Victorian Cervical Cytology Service), Dr Bette Liu (The Sax Institute), Dr Alison Budd (Australian Institute of Health and Welfare), Ms Michelle Bradley (DoHA) and Mr Joel Willis (DoHA) were also involved in this project, reviewing drafts of the manuscript.

Lessons learnt

This project enabled me to learn a number of new skills. Firstly, Aditi introduced me to EpiBasic which is a free data analysis program available for download. It is a useful tool for conducting basic analysis and does not require any syntax. I learnt how to calculate a rate ratio using a post-vaccine period compared to a pre-vaccine period. I also learnt that when interpreting the results of this project, I needed to consider a number of factors. For example, changes in screening participation and sexual

behaviour may be driving the changes in the decline in rate of cervical abnormalities. Additionally, I discovered international screening guidelines recommend that women <25 years of age should not be screened, yet Australia recommends screening at 18 years or two years after sexual debut, whichever is later. I learnt that Australia also screens at a more frequent rate (every two years) than what is internationally recommended (every three years for women under 50 years of age).

Furthermore, I learnt how to format a report to make it look presentable based on a common template used at NCIRS, including how to develop a table of contents in Microsoft Word.

Another important lesson I learnt was the intricacies in obtaining data from reports. It was at times a tedious job that required careful reading of the fine print. It was a new experience for me, as I am used to being provided a dataset however, I have learnt that self-retrieval of data needs to be meticulous to prevent potential errors occurring.

Public health action

The project was conducted to determine if there were any changes in the prevalence of high-grade cervical abnormalities at a national level. The results from this study will form part of the national evaluation of the NHVP which aims to assess how well the NHVP is performing. This has policy implications; if the vaccine program is not performing well; for example, the prevalence of disease has remained unchanged or increased; it gives rise to conducting further analytical studies to determine if the incidence of disease is truly being affected. If further analytical studies produce strong evidence for the success or failure of the NHVP, there is a potential for programmatic change.

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a great deal of expertise into this project. Lastly, I would like to thank Michelle Bradley and Joel Willis for their comments on the draft.

Introduction

Persistent infection with Human Papilloma Virus (HPV) has been found to contribute to nearly all cases of cervical cancer.¹ In Australia, cervical cancer was the twelfth most common cancer among females with 631 incident cases occurring in 2009.^{2,3} Cervical cancer incidence and mortality in Indigenous females has been found to be twice as high than non-Indigenous females.⁴ In June 2006, the quadrivalent HPV vaccine, Gardasil[®] was registered for use in females aged 9–26 years. The following year, the bivalent HPV vaccine, Cervarix[®] was registered for females aged 10–45 years. From mid-2010 the registered indication for Gardasil[®] in Australia was extended to females aged up to 45 years and males aged 9–26 years.⁷

In April 2007, Australia became the first country to implement a fully funded National HPV Vaccination Program (NHVP) for females aged 12–13 years.⁸ In addition, there were two catch-up phases between April 2007 and December 2009 for 13–17/18-year-old females through school-based vaccination programs as well as 18–26-year-old females through general practice and community settings.⁸ The quadrivalent HPV vaccine is being used for the NHVP, offered through state and territory school-based vaccination programs as a course of three injections over six months. A National HPV Vaccination Program Register (NHPVR) was established to record vaccine delivery and allow monitoring of the NHVP.⁹ In February 2013, the program was extended to include males aged 12–13 years as part of the school-based program, with a two year catch-up program for males aged 14–15 years until December 2014.¹⁰

The National Centre for Immunisation Research and Surveillance (NCIRS), as part of its responsibilities under the funding agreement with the Australian Government Department of Health and Ageing (DoHA), has a contractual role in evaluating immunisation programs in collaboration with other stakeholders. As part of the evaluation, the effect of the NHVP on HPV-related cervical abnormalities nationally was assessed in this paper.

Regular Papanicolaou smears ("Pap testing") through the National Cervical Screening Program (NCSP) allow for the early detection and treatment of HPV-related cervical abnormalities prior to the development of cervical cancer. Females are recommended to have regular Pap testing every two years, starting at 18–20 years (for those who ever have been sexually active) or two years after first sexual intercourse, whichever is

later.³ The target age group of the NCSP is females 20–69 years of age.³ Between 2010 and 2011, over 3.7 million females were screened.² During this period, Pap testing detected low-grade cervical abnormalities in approximately 163,050 tests and high-grade cervical abnormalities (HGAs) in a further 58,000 tests.^{2,3} Low-grade abnormalities were found to peak in females aged < 20 years, and HGAs were found to peak in females aged 25–29 years.^{2,3} Under screening guidelines, HGAs must be histologically confirmed prior to the commencement of any treatment.¹¹ Since the implementation of the NHVP in 2007, there has been limited evidence of the effect of HPV vaccine on the incidence of low- and high-grade cervical abnormalities. In the state of Victoria, an analysis of incident cervical abnormalities in the post-vaccination period (1 April, 2007 to 31 December, 2009) compared with the pre-vaccination period (1 January, 2003 to 31 March, 2007) found evidence of a significant reduction in detection of histologically confirmed HGAs in the youngest age group only (< 18 years of age). A significant decrease of 0.38% in incidence of high grade abnormalities in this age group was found in the first two years after the implementation of the NHVP.¹²

The aim of this study was to assess the prevalence of HGAs over time by age group in Australian females eligible and not eligible for the NHVP at a national level and by jurisdiction in women attending for cervical screening. This report provides a summary of cervical screening program statistics across all states and territories in Australia.

Methods

Information was taken from the Australia Institute of Health and Welfare (AIHW) reports *Cervical Screening in Australia* published during 2011–2013.^{2,3,13} All data, including data presented in graphs, are from these reports unless otherwise specified. These reports are compiled using data on the number of females screened and results of screening tests obtained from the eight jurisdictionally based cervical cytology registries ('Pap Test Registers'), all of which report standardised data on a regular basis to AIHW for monitoring of the NCSP. Subsequent results or clinical information received by the registries is not updated to the AIHW.² Data collected from cytology registries aims to monitor the effectiveness of the NCSP using performance indicators for participation, rescreening, cytology, histology, and the cytology-histology correlation.²

The analysis was an ecologic design with comparisons between 2004–2007 and 2008–2011. The years, 2008–2011, were considered as the post-vaccine period as the NHVP commenced in April 2007. The three-dose schedule over a six-month period and the time required for a HPV incident infection to progress to a clinically detected high-grade cervical abnormality would render it extremely unlikely that the vaccine would have any impact on HGAs during 2007.

The annual rate of females attending screening was assessed by age group, using estimated resident population data by jurisdiction and at a national level from the Australian Bureau of Statistics as the denominator. The population was adjusted to include only females with an intact uterus (and cervix) using age-specific hysterectomy fractions derived from the National Hospital Morbidity Database (NHMD).² The NHMD included public and private hospital separations. The majority of females who have had a hysterectomy are not at risk of cervical cancer as their cervix was removed. It is important to note that the NCSP recommends screening biennially and hence report screening participation over two years. In this report, we have calculated annual screening rates to assess whether any changes in screening patterns were occurring on a yearly basis.

Histopathologically defined HGAs included lesions coded as cervical intraepithelial neoplasia of grade 2 (CIN 2) or 3 (CIN 3), adenocarcinoma in situ or endocervical dysplasia. HGAs detected only by cytology were excluded, as a referral for biopsy, with

subsequent histologic examination is routine, following detection of HGA by cytology.¹⁴ Under national guidelines, a female with Pap result of high-grade squamous intraepithelial lesion (including possible) is referred to a gynaecologist for colposcopy and targeted biopsy.¹¹ In Australia, although colposcopy is part of the management of HGAs, histology is considered best practice to confirm HGA.¹¹

Data on numbers of females screened, and numbers of HGAs detected from 2004 to 2011(2004–2007; 2008–2011 and individual years) were tabulated by age groups (<20; 20–24; 25–29; 30–34; 35–69) and by jurisdiction. Trends in rate of HGAs detected were examined. Absolute rates, rate ratios (RR) and 95% confidence intervals were used to quantify changes.

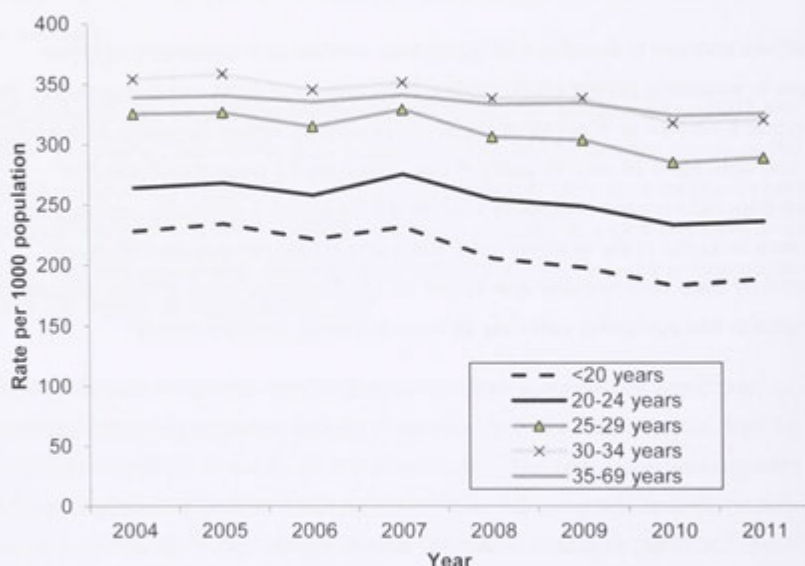
A sensitivity analysis in females < 20 years was conducted to determine whether changes in screening participation affected HGA rates observed in this population. This could occur if women at high risk of abnormalities are no longer screening at the same rates. Females aged 18 and 19 years of age not screened (based on estimated resident population minus number of screened females for a particular post-vaccine year) were included in the analysis using pre-vaccine rates of detected HGA and examined by each post-vaccine year (2008–2011). Expected rates of HGA detected for all females in this age group had they all been screened were calculated.

Results

Annual Screening Rates

Trends in the AIHW data show that annual screening rates among the female population progressively declined, particularly among females <35 years of age. In particular, screening rates among females <20 years, 20–24 years and 25–29 years decreased from 2007 onwards (the year the NHVP commenced); whereas screening rates among females 35–69 years remained relatively constant (**Figure 1**).

Figure 1. Screening rate by age group per 1000 women, 2004–2011



Source: Cervical screening in Australia 2010-2011, AIHW and Australian Bureau of Statistics census data
^ Screening rate per 1000 female population, adjusted for hysterectomy fraction

Overall, screening rates decreased significantly across all age groups when comparing the post-vaccine period with the pre-vaccine period (**Table 1**). The greatest reduction in screening observed was in females <20 years of age. There was a 15% reduction in screening rate during the post-vaccine period compared to the pre-vaccine period. Screening rates in females aged 20–24 years of age and 25–29 years of age decreased by 9% when comparing the post-vaccine period to the pre-vaccine period.

Table 1. Screening rates and rate ratios, by age group, 2004–2011^{†}**

| Age group (years) | Pre-vaccine period 2004-2007 | | | Post-vaccine period 2008-2011 | | | Post-vaccine/ Pre-vaccine |
|-------------------|---------------------------------|---------------|------|----------------------------------|---------------|------|------------------------------|
| | Population | Screened (no) | Rate | Population | Screened (no) | Rate | Rate ratio (95% CI) |
| <20 | 1107561 | 252953 | 22.8 | 1169551 | 226331 | 19.4 | 0.85 (0.84-0.85) |
| 20-24 | 2849997 | 758264 | 26.6 | 3090092 | 746681 | 24.2 | 0.91 (0.91-0.91) |
| 25-29 | 2763886 | 894450 | 32.4 | 3140280 | 923625 | 29.4 | 0.91 (0.91-0.91) |
| 30-34 | 2980738 | 1049064 | 35.2 | 2961738 | 967951 | 32.7 | 0.93 (0.93-0.93) |
| 35-69 | 14972870 | 5068429 | 33.9 | 16056654 | 5261552 | 32.8 | 0.97 (0.97-0.97) |

Source: Cervical screening in Australia 2010-2011, AIHW

[†] ABS population estimates of 18–19 years as denominator for < 20 year age group

^{*} Screening rate per 100 female population per 4-year period

^{**} Comparing 2009-2011 period with 2004-2007 period, by age group, adjusted for hysterectomy fraction

HGAs detected

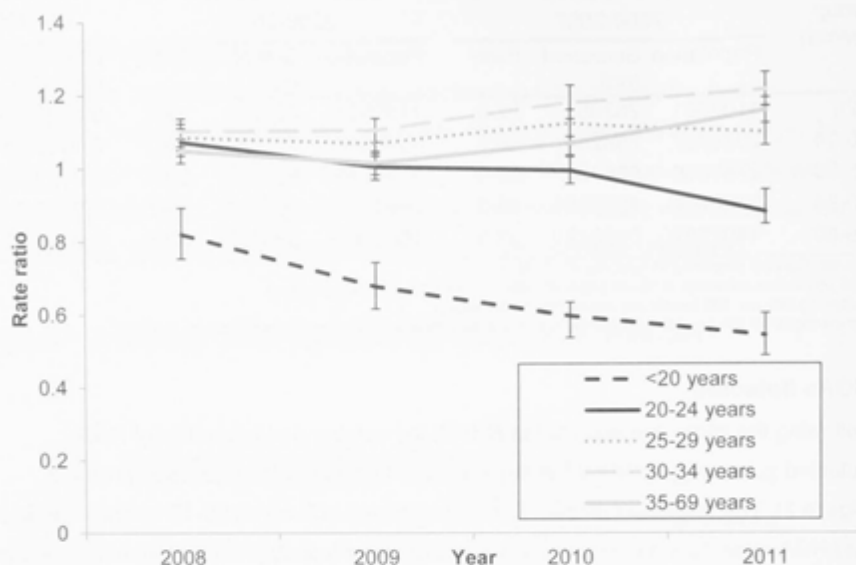
Following the implementation of the NHVP, the number and rate ratios of HGA detected in females aged < 20 years and 20–24 years of age decreased (**Table 2, Figure 2**). The absolute numbers of HGAs detected in females 25–29 years increased and HGA rates during post-vaccine years were significantly greater than during the pre-vaccine year. In the older age groups (30–34 years; 35–69 years), the number of HGAs detected and HGA rate ratio over time increased with each post-vaccine year when compared to the pre-vaccine year. (**See Appendix B1 for rates**).

Table 2. Number of females with high-grade abnormalities detected by histology by age, 2004–2011

| Age group (years) | Year | | | | | | | |
|-------------------|-------|-------|-------|-------|-------|-------|-------|-------|
| | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 |
| <20 | 915 | 851 | 803 | 750 | 653 | 518 | 416 | 385 |
| 20-24 | 3,673 | 3,826 | 3,707 | 3,823 | 4,044 | 3,799 | 3,566 | 3,220 |
| 25-29 | 3,879 | 3,931 | 3,861 | 4,186 | 4,379 | 4,464 | 4,524 | 4,543 |
| 30-34 | 3,111 | 3,127 | 2,945 | 2,933 | 3,126 | 3,155 | 3,201 | 3,378 |
| 35-69 | 4,418 | 4,434 | 4,602 | 4,729 | 4,908 | 4,839 | 5,000 | 5,500 |

Source: Cervical screening in Australia 2010-2011, AIHW

Figure 2. Rate ratio of females detected with a HGA per 1000 females screened by age group, 2008–2011



Source: Cervical screening in Australia 2010–2011, AIHW and Australian Bureau of Statistics census data
 * 95% confidence intervals displayed
 ^ Reference group: 2004–2007 pre-vaccine/baseline period

The most striking reduction was observed in females <20 years, where a reduction in rate of HGA detected occurred during the post-vaccine period compared to the pre-vaccine period (**Figure 2**). Following the introduction of the NHVP, the rate of HGA detected in 2008 was 10.8 (95%CI, 10.0–11.6) per 1000 females screened, an 18% (95% CI: 11%–25%) reduction from the rate during the pre-vaccine period (2004–2007) of 13.1 (95%CI: 12.7–13.6) per 1000 females screened. The rates further declined in 2009 and 2010, with a 33% (95%CI, 26%–39%) and 41% (95%CI, 34%–47%) reduction in rate compared to the pre-vaccine period, respectively. In the most recent post-vaccine year (2011), the most pronounced decline occurred, 46% (95%CI: 40%–51%) lower than the rate during the pre-vaccine period.

Given limited numbers at the jurisdictional level, for example the small populations in the Northern Territory, successive two-year periods (2008–2009 and 2010–2011) were compared with data for 2004–2007 (**Table 3**). At the national level, a significant decline was observed in 2008–2009 compared to 2004–2007, and a further significant decline in detected HGAs per 1000 women screened from 2008–2009 in 2010–2011. When

stratifying by jurisdiction, the rates of HGA detected per 1000 females aged <20 years screened decreased in all jurisdictions by 2010–2011, three years after NHVP commenced (**Table 3**). The Northern Territory (NT) reported the highest rates of HGA of all the jurisdictions during the pre-vaccine period and this remained the case in the post-vaccine periods. Despite the high rates, in 2010–2011 in the NT, a statistically significant 43% reduction (95% CI, 1%–69%) in HGA rate was detected compared to the pre-vaccine period.

Table 3. Rate of HGA detected per 1000 females aged < 20 years screened and 95% confidence intervals by jurisdiction, 2004–2011

| Jurisdiction | Pre-vaccine 2004-2007 | Post-vaccine 2008-2009 | | Post-vaccine 2010-2011 | | Combined post-vaccine period 2008-2011 | |
|--------------|--------------------------|---------------------------|---------------------------------|---------------------------|---------------------------------|--|---------------------------------|
| | Rate (CI)* | Rate (CI)* | Rate ratio (CI) [^] | Rate (CI)* | Rate ratio (CI) [^] | Rate (CI)* | Rate ratio (CI) [^] |
| NSW | 16.2 (15.3-17.2) | 10.8 (9.7-11.9) | 0.66 (0.59-0.75) | 8.2 (7.2-9.2) | 0.50 (0.44-0.58) | 9.5 (8.8-10.3) | 0.59 (0.53-0.65) |
| VIC | 10.8 (9.9-11.7) | 9.7 (8.5-11.1) | 0.90 (0.77-1.06) | 5.9 (4.9-7.0) | 0.55 (0.44-0.66) | 7.9 (7.0-8.8) | 0.73 (0.64-0.84) |
| QLD | 13.6 (12.7-14.6) | 8.8 (7.8-9.9) | 0.65 (0.56-0.74) | 7.9 (6.9-9.1) | 0.58 (0.50-0.68) | 8.4 (7.6-9.2) | 0.62 (0.55-0.69) |
| WA | 10.0 (9.0-11.2) | 8.0 (6.7-9.5) | 0.80 (0.65-0.98) | 7.2 (5.8-8.7) | 0.71 (0.57-0.89) | 7.6 (6.7-8.7) | 0.76 (0.64-0.90) |
| SA | 9.1 (7.8-10.6) | 9.7 (7.7-12.1) | 1.07 (0.81-1.40) | 8.7 (6.8-11.0) | 0.96 (0.71-1.27) | 9.2 (7.8-10.8) | 1.01 (0.81-1.27) |
| NT | 18.5 (12.8-26.1) | 17.8 (13.9-22.5) | 1.04 (0.67-1.60) | 10.1 (5.8-16.5) | 0.57 (0.31-0.99) | 14.6 (10.8-19.3) | 0.82 (0.56-1.02) |
| TAS | 18.1 (15.4-21.2) | 16.8 (12.8-21.5) | 0.93 (0.68-1.25) | 6.0 (3.6-9.3) | 0.33 (0.19-0.53) | 11.7 (9.3-14.6) | 0.65 (0.49-0.85) |
| ACT | 11.7 (8.9-15.0) | 6.2 (3.4-10.4) | 0.53 (0.27-0.96) | 4.1 (1.8-8.1) | 0.35 (0.15-0.74) | 5.2 (3.3-7.9) | 0.45 (0.26-0.74) |
| National | 13.1 (12.7-13.6) | 9.8 (9.3-10.4) | 0.75 (0.70-0.80) | 7.5 (6.9-8.0) | 0.57 (0.53-0.61) | 8.7 (8.3-9.1) | 0.66 (0.63-0.70) |

Source: Cervical screening in Australia 2010-2011. AIHW. Reference group: 2004-2007 pre-vaccine period

* Crude rates are the number of females with high grade abnormalities detected by histology as a proportion of all females screened

At the national level, a progressive reduction in rate of HGA in females aged 20–24 years of age was observed each year since 2008 (**Figure 2**). In 2011, the rate of HGA detected was 17.4 (95% CI 16.8–18.0) compared to 19.8 (95% CI 19.5–20.1) per 1000 females screened in 2004–2007. The first year that a statistically significant decline in rate (12%, 95% CI 9%–15%) in this age group occurred compared to 2004–2007.

Sensitivity Analysis

Expected rates including screened and unscreened (using pre-vaccine rates of HGAs) females <20 years were calculated and were compared with pre-vaccine periods to obtain rate ratios (**Table 4**). From 2009, expected rate ratios were significantly below one demonstrating that the patterns observed were robust to even very large (and implausible) changes in screening practices.

Table 4. Sensitivity analysis of rate ratios of females < 20 years screened, 2008–2011

| A. | B. | C. | D. | E. | F. | G. | H. |
|------|----------------------------------|---|-------------------------|-----------------------------|-------------------------------------|---|-----------|
| Year | No. of females with HGA-screened | Expected no. of HGA by pre-vaccine (2004-2007) rates [^] | No. of females Screened | No. of females not screened | (B+C)/(D+E)x1000 Expected Rates* | Expected Rate Ratio (rate ratio for HGA compared to 2004-7) | 95% CI |
| 2008 | 653 | 3006 | 60,612 | 229142 | 12.63 | 0.96 | 0.92-1.01 |
| 2009 | 518 | 3113 | 58,307 | 238020 | 12.29 | 0.94 | 0.89-0.98 |
| 2010 | 416 | 3151 | 53,297 | 240163 | 12.15 | 0.93 | 0.88-0.97 |
| 2011 | 385 | 3095 | 54,115 | 235895 | 12.00 | 0.91 | 0.87-0.96 |

Source: Cervical screening in Australia 2010-2011, AIHW and Australian Bureau of Statistics census data

* Number of females not screened was calculated by subtracting the number of females screened by ABS population estimates in females 18-19 years

[^] Expected number of HGAs was estimated by multiplying 2004-2007 HGA rates by the number of females not screened

Discussion

National data on the detection of HGAs from a mature and stable screening program provided a well-standardised measure to monitor the occurrence of cervical cancer precursors in the screened female population.

Our analysis indicated that overall, screening rates declined in all age groups, particularly in females <20 years, during the post-vaccine period compared to the pre-vaccine period. The role of vaccination on screening rates was unclear. It is important to note that annual screening rates cannot be interpreted as screening participation given the recommended two-year screening interval. Nevertheless, the decline in screening rate, particularly in females <20 years was unsurprising as participation in cervical screening nationally has gradually declined over time.² This was in line with international experience of a decline in screening participation over the past decade, mostly amongst younger cohorts.¹⁵ The falling screening rates; however, in very young females (<20 years) in Australia are probably not of immediate policy concern, given that Australia screens far younger and more frequently than current International Agency for Research on Cancer (IARC) recommendations. IARC recommends females < 25 years not be targeted based on the potential harm with minimal benefits of screening in this age group.¹⁶ It must be emphasised however, that failure to commence regular cervical screening by a female's mid to late 20s has the potential to result in significant risk, particularly given that many young women vaccinated in the catch up program were already sexually active.¹⁷

The marked decline in screening rate in our study occurred in females <20 years despite campaigns during and after the NHVP, promoting the need still for regular Pap tests.^{12, 18, 19} Concern had previously been raised that a decline in screening participation may occur among females vaccinated against HPV.²⁰ However, in a Victorian study conducted after the implementation of the NHVP, 96% of females aged 18–28 years believed that Pap tests were still required following vaccination.²¹ Only 8% of females who had never had a Pap test before, indicated that the receipt of the HPV vaccine made them less likely to have a Pap test in the future, suggesting it may not be a significant barrier to screening.²¹ Other identified barriers included embarrassment, fear of test result, limited understanding and the lack of information.¹⁹

To determine the relationship between vaccination and screening, the collection of HPV vaccination status in women attending screening may assist in determining

whether there is a significant difference in the proportion of women who do not get screened based on vaccination status. This could ideally occur through data linkage between the NHPVR and the jurisdictional Pap Test Registers. This has recently been conducted in Victoria where the detection rates of HGA were significantly lower in women who received any doses of HPV vaccine compared to unvaccinated women (hazards ratio =0.72, 95%CI 0.58–0.95).²² However, a national-level study is needed to contribute to the evidence of whether there is a relationship between vaccination and screening uptake at a national level.

Additionally, our results showed a substantial decline in the rate of HGA among women <20 years following the implementation of the NHVP, and in 2011, a decline among women aged 20–24 years. There was no decline observed among older women (25+ years). This was consistent with other studies including a Victorian population-based study that found a significant decline in HGA incidence in females <18 years post-2007, however, found no significant change in HGA incidence among women 18–20 years of age ($p=0.7$).¹² This study only utilised data until the end of 2009, during which the catch-up program was still being delivered, and only two years after the implementation of the NHVP. Our analysis included two additional post-vaccine years that captured the 14- and 15-year old age cohorts targeted for HPV vaccine. The findings of a more recent study assessing HPV DNA prevalence in Australian females further supported our results. A large decline in vaccine-type HPV pre-post comparison of 18–24 year olds attending for cervical screening at family planning clinics was observed.²³ Monitoring of HPV DNA prevalence has the potential to provide timely evidence of the impact of HPV vaccine among women who recently have become sexually active.²⁴ Indeed, HPV vaccine effectiveness is lower in older females who are likely to have engaged in sexual activity by the time vaccine was administered.^{25,26} Our analysis found that the reduction in HGA rate was most marked in females < 20 years which may have been influenced by higher vaccine coverage rates reported in younger age groups.²⁷ A significant decline in rate of HGA in females 20–24 years was only observed in 2011. These females would have been 16–20 years of age in 2007 and so many may have been vaccinated around the time of sexual debut¹⁷ compared to the earlier post-vaccine years.

A number of limitations have been discussed previously in using cervical cancer screening program data as a method of assessing the impact of the HPV vaccines.¹² Changes in screening rates, access to screening and screening behaviour have been

described previously as factors affecting the number of lesions detected.²⁴ These factors may be influenced by health promotion campaigns targeting under screened women, which have been demonstrated to increase participation in the Australian setting.²⁸ And which may subsequently raise detection rates, as under-screened women are more likely to have prevalent disease. This may be why a peak in screening rates was observed in 2007, coinciding with the commencement of the NHVP. We were not aware of which jurisdictions ran particular media/health promotion campaigns during the time periods under review, which could have influenced participation and detection rates. Other factors such as prominent media coverage of celebrities with cancer can also affect screening rates in a dramatic fashion. This was observed with the diagnosis and subsequent death of a young British reality television star from cervical cancer in 2008 and 2009, respectively.²⁹ We attempted to consider a scenario whereby including non-screened women, and assumed the same rate of HGA detection as observed in the pre-vaccine period in our analysis. This inclusion was likely to be the most extreme situation, overestimating the rate of HGA detected, as not all females aged <20 years were sexually active. Evidence for this assumption came from a 2008 survey of secondary students in Year 10 and Year 12 in Australia that found that approximately 40% of students had experienced sexual intercourse.¹⁷ Despite this likely overestimation, a reduction in rate of HGA detected was still observed.

Although our analyses identified a significant reduction in rate of HGA in females < 20 years, the known limitations of an ecologically designed study limits our ability to make inferences that the reduction in rates are due to the vaccine. It must also be noted that other factors,^{24, 28} including the change to follow up guidelines for screen-detected abnormalities introduced in 2006,¹¹ may have played a role in the observed declines.

Of all the jurisdictions, the NT had one of the highest rates of HGA in women aged < 20 years and 20–24 years. One explanation for this is that the NT has the highest proportion of Indigenous residents of all the states and territories.³⁰ It has been well-documented that the incidence of cervical cancer is twice as high among Indigenous women compared to non-Indigenous women.³ A study of HPV prevalence in the pre-vaccination period did not find any significant difference in HPV prevalence or prevalence of vaccine preventable types between young Indigenous and non-Indigenous Australian women.³¹ Cofactors such as smoking, other STIs and early age of first pregnancy/high parity may be important in explaining different rates of abnormalities and the development of cancer. Indigenous status is not currently able to be collected in the national cervical screening data. If it could be captured in the future, that would enable research on Indigenous status and cervical screening participation to occur. Variations in HGA rates in jurisdictions may also be due to differences in the completeness of histology reporting from laboratories to the registers or the quality of specimen collection, processing and interpretation. However, the NCSP has standards for laboratories to maintain in relation to the detection rates of HGAs. Monitoring and feedback can result in changes in detection rates from particular laboratories over time, which may have the potential to influence average detection rates.

Another limitation that might exist was including 2007 in the pre-vaccine period, despite the NHVP commencing in April 2007. Given the vaccine schedule and time between exposure and detection of HGA, we concluded that including 2007 in the pre-vaccine period was appropriate. Previous cohort studies have estimated the time between HPV infection and the development of high-grade lesions. A cohort study in the United Kingdom among female 15–19 years found the risk of high-grade cervical intraepithelial neoplasia was 18 times greater in females exposed to HPV (type 16) 6–12 months ago (relative hazards ratio= 18.02 [95% CI= 5.50-59.0]) compared to unexposed females.³² Furthermore, a cohort study in the United States (US) of 241 women identified all HPV associated CIN 2 and 3 detected occurred within the first 24 months of initial detection HPV infection.³³

Conclusions

Our analysis provides the first detailed analysis explicitly analysing cervical screening data, nationally and by jurisdiction, on changes in rates of HGA detected in women following the introduction of the NHVP. The rate of HGA detected in females eligible for HPV vaccination through the national program was found to decline. This was most evident in females aged <20 years, HGA rates were significantly lower following the implementation of the NHVP compared to during the pre-vaccine era, even after accounting for screening participation. While our results are encouraging, the ecological nature of the study prevents definitive conclusions from being made; and there continues to be a need for future analytical studies to be conducted. Ideally, data linkage studies hold the key in providing substantiated evidence of the impact HPV vaccination has on pre-cancerous cervical lesions.

References

1. Schiffman M, Castle PE, Jeronimo J, Rodriguez AC, Wacholder S. Human papillomavirus and cervical cancer. [Review] [172 refs]. *Lancet*. 2007;370(9590):890-907.
2. Australian Institute of Health and Welfare (AIHW). Cervical screening in Australia 2010-2011. Cancer series no.76. Cat. no. CAN 72. Canberra: AIHW, 2013.
3. Australian Institute of Health and Welfare (AIHW). Cervical screening in Australia 2009-2010. Cancer series no. 67. Cat. no. CAN 63. Canberra: AIHW, 2012.
4. Australian Institute of Health and Welfare & Australian Association of Cancer Registries. Cancer in Australia:an overview, 2010. Canberra: AIHW, 2010.
5. Merck Sharp & Dohme (NZ) Limited. Gardasil® Product Information. New Zealand: CSL Biotherapies (NZ) Ltd; 2011.
6. GlaxoSmithKline Australia. Cervarix® Product Information Version 7.0. Belgium: GlaxoSmithKline Biologicals; 2011.
7. Therapeutic Goods Administration. Australian Public Assessment Report for Gardasil. Canberra: Commonwealth of Australia, 2011.
8. Abbott T. Media Release: Government funds Gardasil. Australian Government Department of Health and Ageing; 2006 [cited 2012 9 July]; Available from: [http://www.health.gov.au/internet/ministers/publishing.nsf/Content/487014123B6EBBA1CA257234008126EC/\\$File/abb155.pdf](http://www.health.gov.au/internet/ministers/publishing.nsf/Content/487014123B6EBBA1CA257234008126EC/$File/abb155.pdf).
9. Victorian Cytology Service (VCS). The National Human Papillomavirus (HPV) Vaccination Program Register. 2010 [cited 2011 7 March]; Available from: www.hpvregister.org.au.
10. National Health and Medical Research Council. The Australian immunisation handbook. 10th edition. Canberra 2013.
11. National Health and Medical Research Council. Screening to prevent cervical cancer: guidelines for the management of asymptomatic women with screen detected abnormalities. 2005 [cited 2013 17 Sept]; Available from: <http://www.nhmrc.gov.au/files/nhmrc/publications/attachments/wh39.pdf>.
12. Brotherton JM, Fridman M, May CL, Chappell G, Saville AM, Gertig DM. Early effect of the HPV vaccination programme on cervical abnormalities in Victoria, Australia: an ecological study. *Lancet*. 2011;377(9783):2085-92.
13. Australian Institute of Health and Welfare (AIHW). Cervical Screening in Australia 2008-09. Cat. No. CAN 57 (Cancer series number 61). Canberra: AIHW, 2011.
14. National Cervical Screening Program. An abnormal Pap smear result - what this means for you Canberra: 2006.
15. Lancucki L, Fender M, Koukari A, Lynge E, Mai V, Mancini E, et al. A fall-off in cervical screening coverage of younger women in developed countries. *J Med Screen*. 2010;17(2):91-6.
16. World Health Organization International Agency for Research on Cancer. IARC handbooks of cancer prevention: cervix cancer screening. Lyon: IARC Press, 2005.
17. Smith A, Agius P, Mitchell A, Barrett C, Pitts M. Secondary students and sexual health report 2008, Monograph Series No. 70. Melbourne: Australian Research Centre in Sex, Health & Society, La Trobe University, 2009.
18. Australian Government Department of Health and Ageing. Policy for screening women vaccinated against HPV. Canberra; 2004 [updated 16 May, 2011; cited 2013 3 May 2013]; Available from: <http://www.cancerscreening.gov.au/internet/screening/publishing.nsf/Content/hpv-vaccinated-policy>.
19. PapScreen Victoria. Barriers to screening for women. [cited 2012 31 October]; Available from: <http://www.papscreen.org.au/browse.asp?ContainerID=c14>.

20. Kulasingam SL, Pagliusi S, Myers E. Potential effects of decreased cervical cancer screening participation after HPV vaccination: An example from the U.S. *Vaccine*. 2007;25(48):8110-3.
21. Brotherton JM, Mullins RM. Will vaccinated women attend cervical screening? A population based survey of human papillomavirus vaccination and cervical screening among young women in Victoria, Australia. *Cancer Epidemiol*. 2012;36(3):298-302. Epub 2011/12/30.
22. Gertig DM, Brotherton JM, Budd AC, Drennan K, Chappell G, Saville AM. Impact of a population-based HPV vaccination program on cervical abnormalities: a data linkage study. *BMC Med*. 2013;11:227.
23. Tabrizi SN, Brotherton JM, Kaldor JM, Skinner SR, Cummins E, Liu B, et al. Fall in human papillomavirus prevalence following a national vaccination program. *J Infect Dis*. 2012;206(11):1645-51. Epub 2012/10/23.
24. World Health Organization. Report of the meeting on HPV Vaccine Coverage and Impact Monitoring. Geneva: 2010 16-17 November 2009. Report No.
25. Markowitz LE, Dunne EF, Saraiya M, Lawson HW, Chesson H, Unger ER, et al. Quadrivalent Human Papillomavirus Vaccine: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *Morbidity & Mortality Weekly Report*. 2007;Recommendations & Reports. 56(RR-2):1-24.
26. Markowitz L, Hariri S, Lin C, Dunne EF, Steinau M, McQuillan G, et al. Reduction in Human Papillomavirus (HPV) Prevalence Among Young Women Following HPV Vaccine Introduction in the United States, National Health and Nutrition Examination Surveys, 2003-2010. *J Infect Dis*. 2013;208(3):385-93.
27. Gertig DM, Brotherton JM, Saville M. Measuring human papillomavirus (HPV) vaccination coverage and the role of the National HPV Vaccination Program Register, Australia. *Sex Health*. 2011;8(2):171-8. Epub 2011/05/20.
28. Mullins R, Coomber K, Broun K, Wakefield M. Promoting cervical screening after introduction of the human papillomavirus vaccine: the effect of repeated mass media campaigns. *J Med Screen*. 2013;20(1):27-32.
29. Bowring J, Walker P. The "Jade Goody effect": what now for cervical cancer prevention? *J Fam Plann Reprod Health Care*. 2010;36(2):51-4.
30. Australian Bureau of Statistics. Demographic, social and economic characteristics overview: Aboriginal and Torres Strait Islander people and where they live. 2010 [updated 19 December 2012; cited 2013 16 June]; Available from: <http://www.abs.gov.au/AUSSTATS/abs@.nsf/lookup/4704.0Chapter210Oct+2010>.
31. Garland SM, Brotherton JM, Condon JR, McIntyre PB, Stevens MP, Smith DW, et al. Human papillomavirus prevalence among indigenous and non-indigenous Australian women prior to a national HPV vaccination program. *BMC Med*. 2011;9(1):104.
32. Woodman CB, Collins S, Winter H, Bailey A, Ellis J, Prior P, et al. Natural history of cervical human papillomavirus infection in young women: a longitudinal cohort study. *The Lancet*. 2001;357(9271):1831-6.
33. Koutsky LA, Holmes KK, Critchlow CW, Stevens CE, Paavonen J, Beckmann AM, et al. A cohort study of the risk of cervical intraepithelial neoplasia grade 2 or 3 in relation to papillomavirus infection. *N Engl J Med*. 1992;327(18):1272-8.

Appendix B

B1.1 Rate of cervical high grade abnormalities per 1000 females screened by age group 2004–2011

| Age group (years) | 2004-2007 | 2008 | | 2009 | | 2010 | | 2011 | |
|-------------------|-----------|------|-----------|------|-----------|------|-----------|------|-----------|
| | Rate | Rate | 95% CI | Rate | 95% CI | Rate | 95% CI | Rate | 95% CI |
| <20 | 13.1 | 10.8 | 10.0-11.6 | 8.9 | 8.2-9.7 | 7.8 | 7.1-8.6 | 7.1 | 6.4-7.9 |
| 20-24 | 19.8 | 21.3 | 20.6-21.9 | 19.9 | 19.3-20.6 | 19.7 | 19.1-20.3 | 17.4 | 16.8-18.0 |
| 25-29 | 17.7 | 19.3 | 18.7-19.8 | 19.0 | 18.4-19.5 | 19.9 | 19.3-20.5 | 19.4 | 18.9-20.0 |
| 30-34 | 11.6 | 12.7 | 12.3-13.2 | 12.8 | 12.3-13.2 | 13.6 | 13.2-14.1 | 14.0 | 13.6-14.5 |
| 35+ | 3.6 | 3.7 | 3.6-3.8 | 3.6 | 3.5-3.7 | 3.8 | 3.7-3.9 | 4.1 | 4.0-4.2 |

Chapter 3

Vaccine safety in children and adolescents in Australia: the past, present and future 2000- 2011

Late draft to be submitted to Communicable Diseases Intelligence

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Abbreviations & Acronyms

| | |
|----------------|---|
| ABS | Australian Bureau of Statistics |
| ACSOM | Australian Committee on the Safety of Medicines |
| ACSOV | Australian Committee on the Safety of Vaccines |
| ADRAC | Australian Drug Reactions Advisory Committee |
| ADRS | Australian Drug Reactions System |
| ADRU | Australian Drug Reactions Unit |
| AEFI | Adverse Events Following Immunisation |
| AIHW | Australian Institute of Health and Welfare |
| ANU | Australian National University |
| DAEN | Database of Adverse Events Notifications |
| DoHA | Department of Health and Ageing |
| DTPa | Diphtheria-Tetanus-Pertussis(acellular) |
| dTpa | Adolescent/Adult Diphtheria-Tetanus-Pertussis(acellular) |
| GBS | Guillain-Barré Syndrome |
| Hib | Haemophilus Influenza Type B |
| HepB | Hepatitis B |
| HHE | Hypotonic Hyporesponsive Event |
| HPV | Human Papillomavirus |
| IPV | Inactivated Polio Vaccine |
| IS | Intussusception |
| ISR | Injection Site Reaction |
| MAE | Master of Philosophy (Applied Epidemiology) |
| MenCCV | Meningococcal C Conjugate Vaccine |
| MedDRA | Medical Dictionary for Regulatory Activities |
| NCIRS | National Centre for Immunisation Research and Surveillance |
| NIP | National Immunisation Program |
| OPV | Oral Polio Vaccine |
| PAEDS | Paediatric Active Enhanced Disease Surveillance |
| ph1n1 | Pandemic H1N1 Influenza |
| SAEFVIC | Surveillance of Adverse Events Following Vaccination in the Community |

| | |
|---------------|--|
| TGA | Therapeutic Goods Administration |
| TIV | Tri-valent Influenza Vaccine |
| UNSW | University of New South Wales |
| VAERS | Vaccine Adverse Events Reporting System |
| WAVSS | Western Australian Vaccine Safety Surveillance |
| 4vHPV | 4-valent Human Papillomavirus Vaccine |
| 7vPCV | 7-valent Pneumococcal Conjugate Vaccine |
| 13vPCV | 13-valent Pneumococcal Conjugate Vaccine |
| 23vPCV | 23-valent Pneumococcal Polysaccharide Vaccine |

Abstract

Background:

The surveillance of adverse events following immunisation (AEFI) has existed for many years in Australia. The primary purpose of the surveillance of AEFI is to monitor the safety of vaccines. Ensuring vaccine safety is crucial in instilling confidence in vaccines, particularly in children and infants who are the main receivers of vaccines under Australia's National Immunisation Program (NIP). The objectives of this report were to examine AEFI surveillance data over the past twelve years in infants and children (< 18 years of age).

Methods:

De-identified data were obtained from the Australian Drug Reactions System (ADRS) on all vaccines administered between 1 January 2000 and 31 December 2011 suspected of causing an AEFI in individuals aged under 18 years. Average annual population-based reporting rates were estimated.

Results:

Overall, there were 12,885 reports of AEFI in < 18 years, of which 8.7% were considered serious. Peaks were observed in 2003, 2007, 2008 and 2010 (23.3, 22.0, 22.8 and 60.5 AEFI reports per 100,000 population, respectively). The most marked peak occurred in 2010 following administration with seasonal influenza vaccine. Other peaks occurred following the introduction of vaccines to the NIP, particularly the Meningococcal C Conjugate Vaccine in 2003 (MenCCV) and HPV (Human Papillomavirus) vaccines in 2007.

Conclusions:

The AEFI surveillance system captured a number of signals of AEFI events over the past twelve years. A number of these peaks were considered to be due to increased AEFI reporting following the inclusion of vaccines under the NIP; however the AEFI surveillance system detected the signal of an AEFI event associated with the seasonal influenza vaccine in 2010. A number of limitations, however, exist and improvements including collecting vaccine dosage data and standardisation of reporting are required to enable better interpretation of the data which will enhance the vital role the surveillance system has in ensuring the safety of childhood vaccines.

Prologue

My role

From my practice as a pharmacist, I have always been interested in the monitoring of adverse drug reactions by the Therapeutic Goods Administration (TGA) and the risk assessment procedures that results in a drug being taken off the market. Due to my background, my field placement was keen to get me involved in the Adverse Events Following Immunisation (AEFI) Project Group.

The project on the overview of vaccine safety in Australia (over the past twelve years) commenced early into my placement at NCIRS. Initially, I worked on all AEFI reports between 2000 and 2011, however, the project evolved quickly to have a specific focus on children and adolescents – as they are the receivers of the majority of vaccines under the National Immunisation Program.

I conducted a project proposal for this project and sourced past annual and supplementary reports and TGA documents to gain an understanding of the history of AEFI surveillance in Australia and the many changes that have occurred over the past fifty years. I found this process quite challenging as much of the vaccine safety monitoring was incorporated into general drug safety with no difference in reporting and surveillance between the two. I also conducted a literature review on adverse events associated with specific vaccines and reviewed passive AEFI surveillance systems in the US, Canada and Denmark to consider the differences that existed between them and the Australia system.

Deepika Mahajan, the Senior Research Officer who is responsible for conducting data analyses for AEFI annual and supplementary reports for this project provided me with SAS code that existed for these reports. I adapted these codes for this project and Deepika provided guidance during the data analysis, particularly in understanding the many variables that exist in the database.

I organised and chaired teleconferences that were attended by co-authors for a paper that will hopefully be submitted for publication. Collaborators include NCIRS colleagues (Deepika Mahajan, Aditi Dey, Rob Menzies and Kristine Macartney), TGA staff (Bronwen Harvey) and academics from the University of New South Wales (Glenda Lawrence) and the Australian National University (Stephanie Davis). I produced agendas and wrote minutes during the teleconferences.

A manuscript to be submitted to a peer-reviewed journal has been developed for this project, which is what is presented in this chapter. The manuscript is at a late draft stage with further revisions to be made pending co-author review.

Lessons learned

This project provided me with a range of new skills and experiences that were incredibly valuable. Firstly, I feel this project was a catalyst to making me understand that it is imperative to have clear objectives for each project I commence. It also made me step back and look at the 'bigger picture' and consider the 'so what' factor of what I was doing, particularly for a descriptive study. This was extremely challenging and I still struggled with conceptualising these considerations for subsequent projects, however, I feel that the process itself became habitual, and was probably one of the most important lessons I have learnt during my MAE experience. Furthermore, I learnt that communicating these in the project proposal and having a clear idea of the methodology of this project would have been more efficient, which at times it was not.

Secondly, I believe that the number of iterations that this paper endured allowed me to write better. I learnt that it is important that every paragraph has a 'take home' message.

Further, I learnt so much from collaborating with a number of researchers from different organisations. They were extremely forthcoming in providing their expert knowledge on AEFI to me and I tried to absorb as much as I could from them. Indeed, I learnt that AEFI surveillance is complex and trying to understand the operation of the surveillance system was somewhat challenging.

One important lesson learnt was diplomacy when working with a number of collaborators from different organisations. It was also a good experience to navigate the paper to ensure that all co-authors were content with what was produced and also learn to facilitate teleconferences among collaborators.

Lastly, this project taught me many things about mentoring students. I received a great deal of support from different individuals for this project and it has provided me with important insight on how I hope to be if I was to supervise or mentor students in the future.

Public health action

This project describes the past and present of vaccine safety monitoring in children and adolescents which has policy implications for future vaccine safety. It addresses a number of

limitations of vaccine safety monitoring and suggests possible methods to improve the system. Through descriptive analysis, it provides evidence of the importance of the passive surveillance system in allowing for signal detection and hypothesis generation. This project identifies passive surveillance as an vital component of vaccine safety monitoring in Australia.

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Introduction

In Australia, post-marketing surveillance and monitoring of medicines, including vaccines, has existed for many years through a passive surveillance system.¹ The Australian regulatory authority, the Therapeutic Goods Administration (TGA) is responsible for regulating medicines, including vaccines, and for monitoring their safety once they are available on the market.² Nationally, passive surveillance relies on the voluntary reporting of suspected adverse events from vaccines to the TGA. An Adverse Event Following Immunisation (AEFI) is defined as any serious or unexpected adverse event following vaccination that may be from the vaccine itself or its handling and administration; it can be coincidentally associated with the timing of vaccination.³ The surveillance of Adverse Events Following Immunisation (AEFI) primarily functions to: detect signals of suspected adverse events that were not detected during pre-licensure trials; identify any changes in rates of known adverse events; and to detect adverse events associated with program errors. This will ensure appropriate public health action is initiated.

At present, Australia is one of the few countries⁴⁻⁶ in the world with a comprehensive immunisation program— the National Immunisation Program (NIP). Under the NIP, certain immunisations are provided free of charge to eligible Australians by the federal government (**Table 1**).^{1, 3, 7-13} Instilling public confidence in the NIP is an important contribution of AEFI surveillance.^{1, 7} Over time, the number of vaccines recommended on the NIP schedule has increased. In 2000, there were 16 vaccines included in the NIP schedule to protect against seven diseases¹⁴ in child and school programs compared to the 19 vaccines recommended to protect against 14 diseases in child and school programs in 2013.¹⁵ With the addition of new vaccines on the schedule, it is imperative that vaccine safety monitoring occurs. This is particularly the case as nearly a quarter of parents have been found to believe children receive too many vaccines.¹⁶

Table 1: History of the schedule changes to the National Immunisation Program in children and adolescents 2000- 2011

| Year | Month | Intervention |
|------|-----------|--|
| 2000 | March | Haemophilus B (Hib) vaccine funded; infants 2,4,6, 12 months |
| | May | Hepatitis B (HepB) vaccine funded; birth followed by 3 HepB doses of combined vaccine |
| 2001 | May | Three doses of 7-valent Pneumococcal Conjugate Vaccine (7vPCV) funded for children at highest risk for Invasive Pneumococcal Disease)* |
| | | A 7vPCV catch-up program became funded [^] A single dose of 23-valent Pneumococcal Polysaccharide Vaccine (23vPPV) funded and recommended [†] |
| 2003 | January | A single dose of meningococcal conjugate vaccine (MenCCV) recommended and funded; infants 12 months |
| | | MenCCV catch-up program funded for all children; children 2-19 years |
| | September | 4th dose of diphtheria, tetanus, acellular pertussis (DTPa) at 18 months of age removed from the NIP schedule |
| | September | A single dose of varicella vaccine recommended at 18 months of age; A single dose of varicella vaccine recommended for children aged 10–13 years with no history of varicella vaccination or clinical disease |
| 2004 | January | dTpa funded for adolescents, the eligible age group varied in different jurisdictions |
| | June | dTpa-IPV vaccine registered, for use in individuals aged ≥4 years |
| 2005 | January | 7vPCV program; all infants 7vPCV catch-up program; < 2 years |
| | November | Inactivated Polio Virus (IPV) became funded to replace Oral Polio Vaccine (OPV) Combined DTPa-hepB-IPV-Hib vaccine used in ACT, NSW, TAS and WA (for non-Indigenous children); DTPa-IPV vaccine used in other jurisdictions and in Aboriginal and Torres Strait Islander infants in WA Funded national varicella program commenced; 18 months of age |
| 2006 | February | Funded school-based varicella catch-up program commenced, with routine vaccination for one cohort of children aged 10–13 years with no history of varicella vaccination or clinical disease |
| | October | Recommendation and funding of a 2 dose schedule of monovalent rotavirus vaccine and 2 and 4 months in infants using monovalent rotavirus vaccine (NT only) |
| 2007 | April | 4-valent human papillomavirus vaccine (4vHPV) funded for females aged 12-13 years- school-based program |

| | | |
|------|-----------|--|
| | July | 4vHPV catch-up program :females 13-26 years- schools or primary care providers |
| | | Funded national immunisation commenced, using a 2-dose schedule of monovalent rotavirus vaccine (2 and 4 months; ACT, NSW, NT, TAS, WA) or a 3-dose schedule of pentavalent rotavirus vaccine (2, 4 and 6 months; QLD, SA, VIC) |
| 2008 | March | Seasonal influenza vaccination program commenced (6 months – 5 years)–WA only |
| | | Queensland, South Australia and Victoria changed to a single hexavalent DTPa-IPV-HepB-Hib vaccine after using two combination vaccines (quadrivalent DTPa-IPV and Hib-HepB). |
| 2009 | May | WA changed from using a 2-dose schedule of monovalent rotavirus vaccine to using a 3-dose schedule using pentavalent rotavirus vaccine |
| | September | A single dose of pandemic H1N1 influenza (pH1N1) vaccine funded children; ≥ 10 years |
| | October | 10valent PCV funded; infants 2,4,6,18 months of age (replaced 7vPCV) in the NT* |
| | | Due to an international shortage of PedvaxHib® (Hib) and Comvax ® (Hib-HepB) all States and Territories were using the single hexavalent Infanrix hexa® (DTPa-IPV-Hib-HepB) vaccine for all children at 2, 4 and 6 months of age |
| | December | 4vHPV catch-up program ceased |
| | | A two-dose schedule of pH1N1 vaccine funded; children 6 to ≤ 9 years |
| 2010 | January | Trivalent Influenza Vaccine (TIV) funded children; ≥ 6 months with medical risk factors and all Indigenous individuals ≥ 15 years |
| | April | Use of TIV children < 5 years suspended |
| | June | 4vHPV registered for use in males aged 9–26 years |
| | August | TIV < 5 years resumed excluding 1 brand (Fluvax, CSL Biotherapies) no longer for use in children aged 6 months to <5 years) |
| | December | Pandemic (A/H1N1 2009) influenza vaccine no longer available |
| 2011 | July | 13-valent Pneumococcal Conjugate Vaccine (13vPCV) replaces 7vPCV; infants 2,4,6 months |
| | | 13vPCV funded; children 12-35 months who completed primary 7vPCV course. |
| | October | 13vPCV replaced the 10vPCV for use in the NT. A supplementary dose of 13vPCV was provided to those who had received the 10vPCV |
| | | 23vPPV booster dose for Aboriginal and Torres Strait Islander children aged 18–24 months living in NT, SA, QLD and WA ceased, following implementation of the 13vPCV catch-up program for children aged 12–35 months |

* all Aboriginal and Torres Strait Islander infants, all children with specified underlying medical conditions that predispose them to invasive pneumococcal disease, and non-Indigenous children residing in Central Australia

^ non-Indigenous children residing in Central Australia <2 years of age, Aboriginal and Torres Strait Islander children in Central Australia <5 years of age, and Aboriginal and Torres Strait Islander children in northern NT <2 years of age

† Aboriginal and Torres Strait Islander children aged 18–24 months living in NT, SA, QLD, WA after completion of primary 7vPCV 3-dose course. Children with specific underlying medical conditions aged 12 months following completion of primary 7vPCV 3-dose course. School children aged 15–19 years (Grade 10 and 12) in the NT (changed to Grade 11 and 12 in 2002).

+ all children in the NT at age 2, 4, 6 and 18 months of age, replacing the use of the 7vPCV (3 doses) with or without a booster dose of 23vPPV

Surveillance of AEFI in Australia has evolved from a reporting scheme which initially involved only doctor as reporters,¹⁷ to surveillance encompassing passive, enhanced and active approaches with numerous reporter types (e.g. general public and state and territory health departments).^{3, 18, 19} In 2000, the Adverse Drug Reactions Unit (ADRU) of the TGA became responsible for collating and reviewing all AEFI notifications.¹ An expert committee of the TGA, the Adverse Drug Reactions Advisory Committee (ADRAC) would meet at six-weekly intervals to consider and discuss concerning AEFI reports.¹ Since then, minimal changes the passive surveillance remained somewhat unchanged, however in 2010, structural changes led to the Office of Product Review replacing ADRU and the Advisory Committee of the Safety of Medicines (ACSOM) replacing ADRAC as the expert advisory committee.²⁰ Since 2002, the National Centre for Immunisation Research and Surveillance (NCIRS) became responsible for analysing data, producing routine reports and also ad-hoc reports for AEFI when requested under an agreement with the TGA.¹ In 2013, following recommendation of a review of passive surveillance of AEFI in Australia, the Advisory Committee on the Safety of Vaccines (ACSOV) was formed. This statutory expert committee's role is to advise and provide recommendations to the Minister of Health on vaccine safety Australia including conducting risk assessments and risk management.²¹

Some diversity of vaccine safety monitoring exists between states and territories. AEFIs can be notified through a number of different mechanisms.²² In 2007, the state of Victoria established an enhanced passive surveillance system, the Surveillance of Adverse Events Following Vaccination in the Community (SAEFVIC).¹⁹ More recently, the Western Australian Vaccine Safety Surveillance (WAVSS), based on the SAEFVIC model, was established in the state of Western Australia.²³ A recent study found that the reporting rate of AEFI increased in Victoria from 2.6 per 100,000 population (2003) to 13.5 per 100,000 population (2009) following the implementation of SAEFVIC.¹⁹ Additionally, the Paediatric Active Enhanced Disease Surveillance (PAEDS) project is a hospital based surveillance system in five hospitals across the country that can detect AEFI. Detailed clinical information and

biological samples are collected for some vaccine-related childhood conditions (intussusception, infantile seizures, acute flaccid paralysis and severe complications of varicella).¹⁸

Similarly, passive AEFI surveillance systems exist in Canada and the USA, which also collate voluntary reports of AEFI at a national level.^{24, 25} The American system– the Vaccine Adverse Events Reporting System (VAERS) was established in 1990 and accepts AEFI reports via the internet, mail or fax from health professionals, vaccine manufacturers, and the general public and are entered into the VAERS database.²⁴ In Canada, the Canadian Adverse Events Following Immunization Surveillance Systems (CAEFISS) nationally collates voluntary reports from clinicians and also the general public.^{25, 26} Both countries also supplement their passive surveillance systems with enhanced and active systems.

In Australia during 2010, an unexpected increased risk of febrile convulsions in children aged less than 5 years of age occurred in association with one brand of seasonal trivalent influenza vaccine (TIV) that had been used in Australia for many years. The events leading up to and surrounding the temporary nationwide suspension of influenza vaccine use in this age group, while evidence implicating one, but not the other registered vaccine brands was gathered, led to a national and state-based review of the surveillance system/s for monitoring vaccine safety in Australia.^{27, 28} Recommendations from the national review have been adopted and will result in a number changes to the current system to further enhance vaccine safety surveillance.²⁹

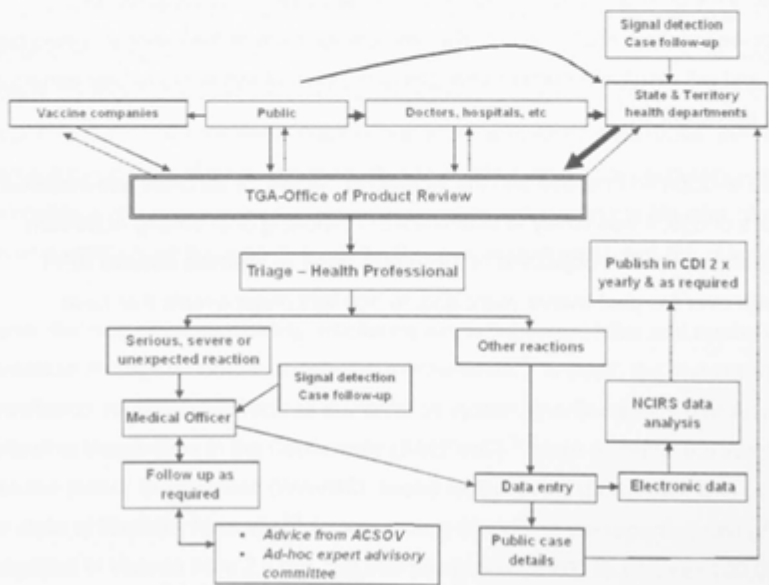
In light of these anticipated changes and the increasing number of vaccines administered to those < 18 years of age, it was timely to examine AEFI reporting data among Australian children and adolescents. The objectives of this report were: to examine passive AEFI surveillance data over the past twelve years and; to highlight major events that have occurred.

Methods

System description

The mechanisms to report AEFI and the types of reporters of AEFI have been described previously.¹ In short, all reports are forwarded, either directly by the individual reporter or by the jurisdictional health department, or in Tasmania's case, directly to the TGA where they are assessed using internationally consistent criteria³⁰ and then entered into the Australian Adverse Drug Reaction Reporting System (ADRS) database (**Figure 1**). Information of the severity of outcome of the AEFI was collected, and included non-serious, not recovered at the time of reporting and serious. An AEFI is defined as 'serious' if the reaction meets one of more of the following: 1) Results in death; 2) Is life-threatening; 3) Requires inpatient hospitalisations or prolongation of existing hospitalisations; 4) Results in persistent or significant disability or incapacity; 5) Is a congenital anomaly/birth defect and; 6) Is a medical important event or reaction. It was assumed that AEFIs assigned as not-recovered during the time of reporting were not serious.

Figure 1:Reporting pathway of the AEFI passive surveillance system, adapted from TGA



It is possible that a single adverse event can result in more than one notification/record being generated in the ADRS database thus the term 'AEFI record' is used. Records of AEFI

typically list signs, symptoms and/or diagnoses that are coded by the TGA into standardised lower level terms (LLT) and an equivalent preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA).³¹ MedDRA classifies adverse events using a hierarchical five-level structure from the highest level 'system organ class' (e.g. skin and subcutaneous disorders) to LLT, the lowest level (e.g. bruising of face).³² Each LLT is related to only one PT (second lowest level terminology). A PT is a single medical concept and is specific enough that pathologic or etiologic information is detailed (e.g PT= Rhinitis seasonal versus PT= Rhinitis perennial).³²

Records of AEFI were assigned into 'certain', 'probable' and 'possible' causality ratings by medical officers at the TGA. This method of rating causality has been described previously.

¹³ Causality can be difficult to establish, particularly when multiple vaccines are co-administered (which often occurs in children). When a systemic adverse event occurs in this instance, all vaccines co-administered are usually listed as 'suspected' of involvement.

Data used

We used de-identified AEFI data obtained from the ADRS database provided by the TGA in September 2012.³³ All vaccines administered between 1 January 2000 and 31 December 2011 that were 'suspected' of causing the AEFI were included in our analysis. Where date of vaccine administration was missing, onset date of symptoms or signs was used. Records were only included for those less than 18 years of age.

Data Analyses

Data analyses were performed using SAS ® (version 9.3, SAS Institute, Cary, NC, USA).³⁴ Descriptive analyses were conducted to determine the crude number of AEFI records per year and numbers were further stratified by: age group; sex; level of seriousness; vaccine type; jurisdiction; reaction type; reporter type (state and territories, immunisation providers, vaccine sponsors, public and other) and; causality(certain, probable, possible). Population estimates were obtained from the Australian Bureau of Statistics (ABS) to estimate average annual population-based reporting rates.³⁵

Results

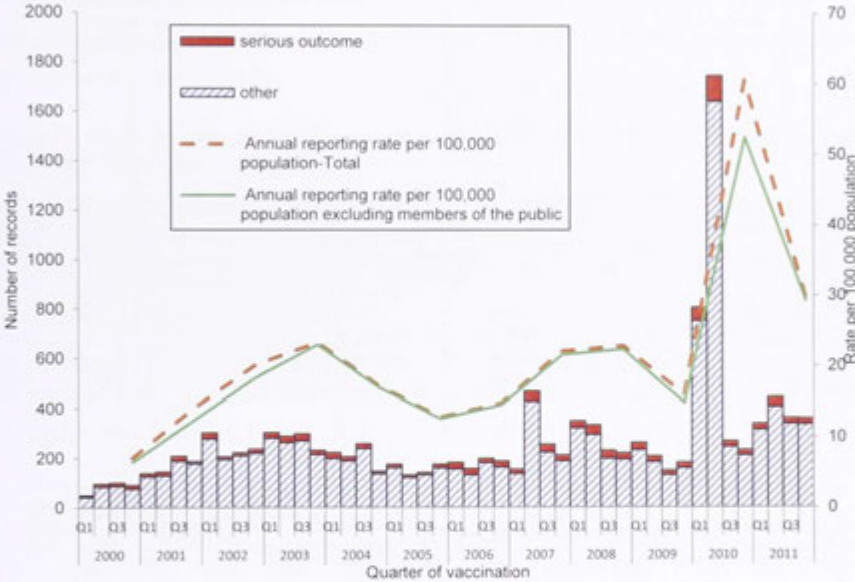
Overall, there were 12,885 records of AEFI reported in the passive AEFI surveillance system in children under 18 years of age between January 1, 2000 and December 31, 2011. Of these 1119 AEFIs (8.7%) were recorded as serious (**Table 2**) and 72.3% had a 'possible' causal rating for the vaccine resulting in an adverse event. Females accounted for 6,263 reports (48.6%). AEFI reports did not appear to differ by sex except for a higher proportion of adolescent (11–17 years) AEFI reports occurring in females (75.2%). States and territories were the main reporters of AEFI (68.3%) followed by GPs (13.1%). The public accounted for 5.3% of all reports.

Table 2. Characteristics of AEFI reports in children < 18 years; 2000–2011

| | Number | Proportion (%) |
|--|--------|----------------|
| AEFI reports | 12885 | |
| Median age (years) | 3 | IQR: 1-5 |
| Sex | | |
| Male | 5986 | 46.5 |
| Female | 6263 | 48.6 |
| Unknown | 636 | 4.9 |
| Seriousness | | |
| Not serious | 8020 | 62.2 |
| Serious | 1119 | 8.7 |
| Not recovered at the time of reporting | 2146 | 16.7 |
| Missing | 1600 | 12.4 |
| Causality | | |
| Possible | 9316 | 72.3 |
| Certain/ probable | 3569 | 27.7 |
| Reporter type | | |
| State/Territory | 8800 | 68.3 |
| General Practitioners | 1684 | 13.1 |
| Hospital | 954 | 7.4 |
| Public | 678 | 5.3 |
| Nurse | 441 | 3.4 |
| Drug company | 184 | 1.4 |
| Pharmacist | 81 | 0.6 |
| Specialist | 45 | 0.4 |
| Other | 14 | 0.1 |
| Missing | 4 | 0.03 |

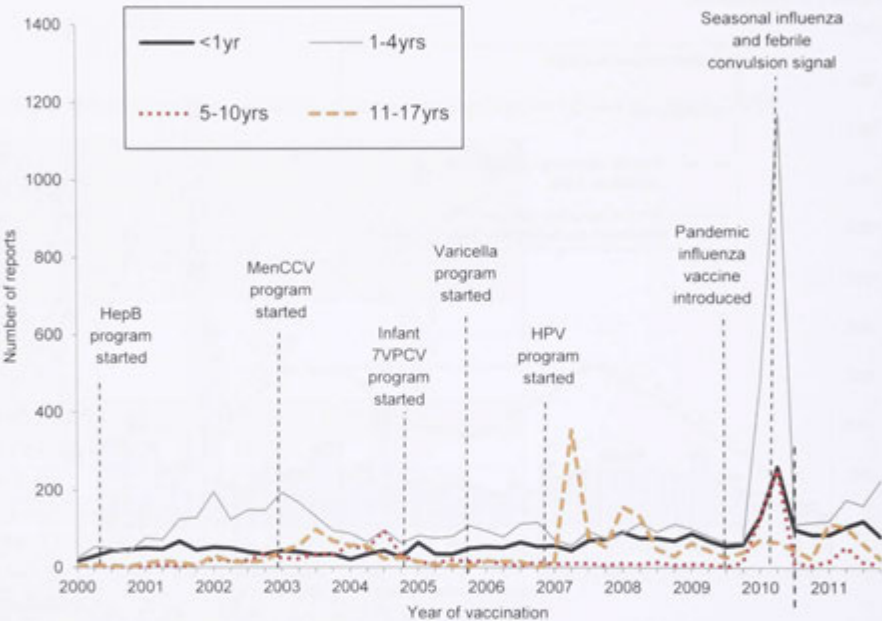
The annual reporting rate of AEFIs fluctuated during this period (**Figure 2**). In 2000, there were 7.0 AEFI records per 100,000 population and peaks were observed in 2003 (23.3 per 100,000 population), 2007 (22.1 per 100,000 population) and 2008 (22.8 per 100,000 population). In 2010, a substantial increase in reporting rate was observed (60.6 per 100,000 population). Reporting rates including and excluding the public as reporters (**Figure 2**) were nearly identical except in 2010, when public reporting was higher.

Figure 2: Adverse events following immunisation, 2000-2011 by quarter < 18 years; 2000-2011, Australia



The greatest numbers of AEFI records occurred in the 1–4 year age group (Figure 3). AEFI reporting increased following the inception of the MenCCV program (offering one dose for all 1–19 year olds from 2002) and the HPV vaccine program (2007). Overall, 73% of AEFI records in < 18 years occurred in children < 4 years (< 1 year; 23% and 1–4 years; 50%). A peak of AEFI records among adolescents (11–17 years) was observed in 2007 (Figure 3).

Figure 3: Number of AEFI reports by age group in < 18 years; 2000–2011, Australia



The most common AEFI recorded was injection site reaction (n=3998) followed by pyrexia (n=3886) and rash (n=1676) (**Table 3**)

There were 287 cases of Hypotonic Hyporesponsive Episode (HHE), of which 83% (n=240) occurred in infants (< 1 year) and 16% (n= 46) records in children aged 1–4 years. Sixty-one cases of intussusception (IS) were reported during the 12 year period of which 98% (n=60) occurred in infants. There were 173 reports of febrile convulsions, most common in children aged 1–4 years (72.8%; n=126) followed by infants (24.9%; n=43).Forty-two reports of anaphylactic reaction occurred over the twelve year period; 43% (n=18) reportedly occurring in adolescents (11–17 years) followed by 33% (n=14) in children aged 1–4 years. There were 284 reports of syncope during this period, 71.5% (n=203) of reports occurred in adolescents (11–17 years).

Table 3. Type of selected AEFI reports by preferred terms by age groups in children < 18 years; 2000–2011, Australia

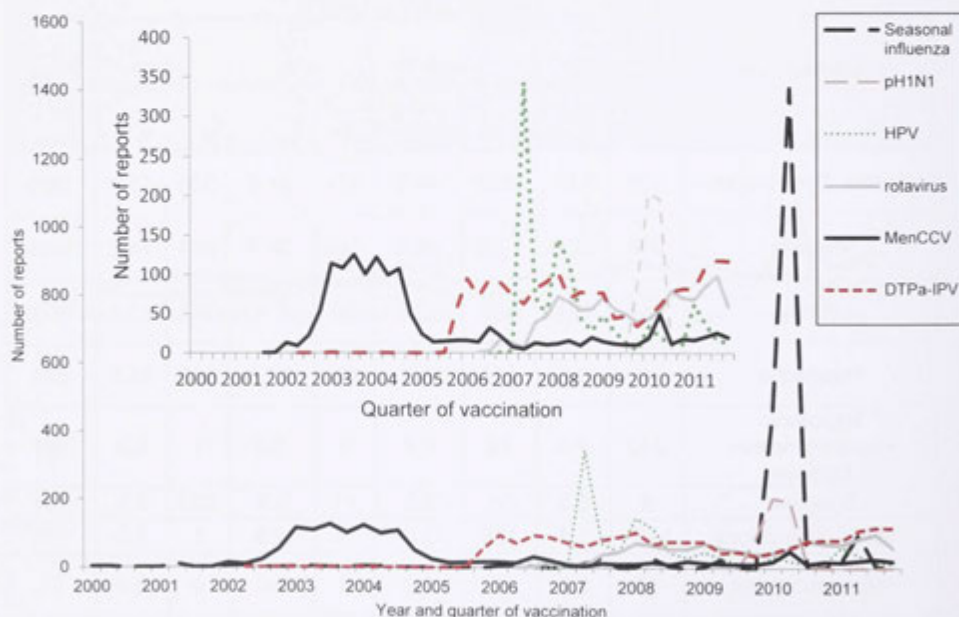
| | Age group (years) | | | | | | | | |
|----------------------------------|-------------------|------|------|------|------|------|-------|------|-------|
| Preferred term | < 1 | | 1-4 | | 5-10 | | 11-17 | | Total |
| | n | % | n | % | n | % | n | % | |
| Injection Site Reaction | 403 | 13.3 | 2838 | 44.3 | 421 | 34.6 | 336 | 15.0 | 3998 |
| Pyrexia | 843 | 27.8 | 2279 | 35.6 | 446 | 36.7 | 318 | 14.2 | 3886 |
| Rash | 544 | 18.0 | 695 | 10.9 | 90 | 7.4 | 347 | 15.5 | 1676 |
| Headache | 4 | 0.1 | 144 | 2.3 | 207 | 17.0 | 515 | 23.0 | 870 |
| Hypotonic Hyporesponsive Episode | 240 | 7.9 | 46 | 0.7 | 0 | 0.0 | 1 | 0.0 | 287 |
| Syncope | 9 | 0.3 | 31 | 0.5 | 41 | 3.4 | 203 | 9.1 | 284 |
| Febrile convulsions | 43 | 1.4 | 126 | 2.0 | 3 | 0.3 | 1 | 0.0 | 173 |
| Intussusception | 60 | 2.0 | 1 | 0.0 | 0 | 0.0 | 0 | 0.0 | 61 |
| Anaphylactic reaction | 5 | 0.2 | 14 | 0.2 | 5 | 0.4 | 18 | 0.8 | 42 |
| Thrombocytopenia | 5 | 0.2 | 13 | 0.2 | 1 | 0.1 | 3 | 0.1 | 22 |

Severity of outcome

Over the 12 year period, 62% (n=8020) of AEFI reports were defined as 'non-serious' and 16.7% (n=2146) were defined as not recovered at the time of the report. Sixteen deaths (0.12%) were temporally associated with receipt of vaccine however the causality rating for all deaths was 'possible'.

Vaccine types suspected of causing an AEFI in children and adolescents are displayed (Figure 4). A substantial peak associated with seasonal influenza vaccine occurred in 2010. During the same year a peak in AEFI reports associated with pH1N1 also occurred. AEFI reports associated with rotavirus increased after-2007. MenCCV associated AEFI peaked in 2002–2004 and then declined from 2005. Similarly, HPV vaccine associated AEFI reporting peaked in 2007, however, in more recent years, has declined.

Figure 4: Number of vaccine-specific AEFI records by vaccines in < 18 years; 2000-2011, Australia



Discussion

Passive post-marketing surveillance is an important component of monitoring vaccine safety as pre-licensure trials have insufficient numbers of participants to identify rare and serious adverse events.³⁶ Our report provides a description of passive AEFI surveillance over the past twelve years in Australian children and adolescents. Over the study period, a number of peaks were detected. These represent both adverse events associated with specific vaccines, and what are most likely artefacts of vaccine programs.

Between 2000 and 2011, the most striking peak was the 2010 peak associated with TIV, showing that the passive surveillance system was able to capture a signal of a true adverse event. Since its registration in Australia, no safety issues associated with TIV had occurred until 2010 when an unexpected safety signal was detected in Western Australia. An increase in the number of emergency department presentations in children with high fever and febrile convulsions was detected following receipt of TIV.³⁷ More in-depth investigation alerted the TGA to conduct an investigation which subsequently led to the suspension of all brands of seasonal influenza vaccine in children under 5 years of age.²⁹ The vaccine was subsequently suspended by the Chief Medical Officer for children aged 5 years and under, pending a national investigation into the issue.²⁹ Further investigations identified receipt of a specific brand of influenza vaccine to be significantly associated with these adverse events.³⁷ Following this, a review of the passive AEFI surveillance system and its ability to respond to this event was undertaken. The review recommended numerous improvements to the system including a more consolidated, systematic approach in reporting AEFI.²⁹

A number of other peaks were also observed during the study period. It is probable that most of these peaks were attributable to the 'Weber' effect,³⁸ as increased reports occurred immediately following the introduction of a new vaccine onto the NIP. The high proportion of AEFI records in females from the 11–17 year age group, which peaked in 2007, was likely due to the introduction of the HPV vaccine offered only to females and not males. The increase in vaccine-specific AEFI reporting rates has been observed internationally, following the introduction of new vaccines including varicella, HPV and 7-valent pneumococcal vaccines.³⁹⁻⁴¹

Reporting rates of AEFI by vaccine dosage is important in inferring whether a vaccine is indeed associated with an AEFI. Australia was the first country to establish a centralised Australian childhood immunisation register (ACIR) in children aged <7 years in 1996.⁴² The number of vaccine doses from ACIR is used to calculate AEFI rates per vaccine dose given,

allowing for the monitoring of trends. Currently, an estimated 99% of all children in the population are registered; a near-complete population register.⁴³ However, there is evidence of underestimations in vaccine coverage.⁴⁴ Furthermore, although vaccination records remain on the register indefinitely, once a child has their seventh birthday no new vaccine records are added.⁴³ For older age groups, the only source of vaccine coverage data is from school-based programs or surveys or jurisdictional immunisation registers. Given the lack of consistent coverage data for the age range used in this study, rates were reported per 100,000 population and cannot be interpreted as incident rates per vaccine doses given which makes detecting a signal challenging. For example, a peak in AEFI may be correlated with an increase in vaccine doses rather than a true AEFI event. To enable better interpretation of passive surveillance data in Australia, an expanded immunisation register for all children under 18 years of age would allow for incident rates of AEFI to be calculated per vaccine doses given as in the Netherlands (where a register exists for individuals up to 19 years of age).⁴⁵ Expanding Australia's immunisation register to include individuals > 7 years would enable reporting rates of AEFI to be calculated, strengthening surveillance.

Not all AEFIs however can be detected by the AEFI surveillance system; particularly rare events such as intussusception. Between 2000 and 2011, there were 61 cases of IS detected nationwide by this system. This was an underestimate as evidenced by the Paediatric Active Enhanced Surveillance System (PAEDS) that captured 132 cases of IS between 2000 and 2006 in four states of Australia.⁴⁶ This demonstrated the relative lack of sensitivity of the passive AEFI surveillance system to detect rare AEFIs and the importance of complementary surveillance systems.

Another limitation of the AEFI surveillance system is that it is possible that biased reporting of suspected AEFI is occurring, for example more serious AEFIs may be reported more than less serious AEFI, however majority of cases that were reported were 'non-serious' events. Co-administration of multiple vaccines also may lead to difficulties identifying a particular vaccine to an adverse event. Additionally, individual AEFI notifications vary considerably in data completeness and quality resulting in difficulties analysing data. For example, it is expected that reports from the public would vary in quality to reporting conducted by healthcare practitioners as would the level of information provided by the reporter. Furthermore, coding errors may occur resulting in potential misclassification of exposure or outcome variables. Reporting forms for AEFI also differ by jurisdiction, making consolidation and interpretation of data extremely challenging. Forms vary in responses from free text responses to tick box responses. A previous New Zealand study found that opened

ended questions used to describe reactions has been found to lead to difficulties in recording AEFI.⁴⁷ The lack of a standardised reporting form has been highlighted as a major limitation in the collection of AEFI data ultimately compromising internal validity.²⁹

Despite these limitations, the surveillance system serves as a national data source that records information on reaction types and vaccines administered. Further, following the review of Australia's response to the 2010 seasonal influenza vaccine event, numerous recommendations to improve vaccine safety were formulated. These recommendations have resulted and continue to result in changes to the passive AEFI surveillance system.²⁹ This includes the development of a standardised AEFI reporting form, consistent case definitions and the need to improve vaccine dosage data.

To this point, we have discussed the limitations of the AEFI surveillance system in the context of reporting and data, however it is also important to note another limitation. The lack of transparency in the system during the review was considered a key limitation in the system, i.e. the delay to the public in being alerted to a AEFI and an understanding of the vaccine safety surveillance processes.²⁹ To improve transparency, the Database of Adverse Event Notifications (DAEN) was launched in August 2012. DAEN is a searchable database available online to the public and contains reports of all adverse event reports for medicines (including vaccines).⁴⁸ These reports are from a wide range of sources.⁴⁸ For vaccines, individual reported adverse events are reviewed by the TGA and relevant information is copied from the internal TGA database (ADRS) to the DAEN.

Despite the limitations, it is important to note the strengths of the AEFI passive surveillance system for monitoring vaccine safety. It is a well-established system that collects detailed information on AEFI including demographics and vaccines administered from a diverse range of reporters. It has shown that it has been able to capture events of public health significance. With a number of improvements, the passive surveillance system has the potential to be better utilised and hence of even greater value.

Conclusion

AEFI passive surveillance is an essential component of the NIP. It has contributed to vaccine safety over the past 12 years, including detecting signals of increased reports of AEFI. Improvements in capturing vaccine dosage data and standardising reporting forms has the capacity to further strengthen the passive surveillance system as a vital component of vaccine safety and a complements other AEFI surveillance systems in Australia.

References

1. Lawrence G, Menzies R, Burgess M, McIntyre P, Wood N, Boyd I, et al. Surveillance of adverse events following immunisation: Australia, 2000-2002. *Communicable Diseases Intelligence*. 2003;27(3):307-23.
2. Department of Health and Ageing Therapeutic Goods Administration. Adverse drug reactions: Australian Statistics on Medicines 2010. 2011.
3. Mahajan D, Cook J, Dey A, Macartney K, Menzies RI. Annual report: surveillance of adverse events following immunisation in Australia, 2011. *Communicable Diseases Intelligence*. 2012;36(4):E315-E31.
4. Public Health Agency of Canada. Publicly funded Immunization Programs in Canada - Routine Schedule for Infants and Children including special programs and catch-up programs (as of March 2013). 2013 [updated 26 April 2013; cited 2013 1 May]; Available from: <http://www.phac-aspc.gc.ca/im/ptimproq-progimpt/table-1-eng.php>.
5. ACIP Childhood/Adolescent Immunization Work Group. Advisory Committee on Immunization Practices (ACIP) Recommended Immunization Schedule for Persons Aged 0 Through 18 Years — United States, 2013. *MMWR*. 2013 28 January;62.
6. Ministry of Health. Immunisation Handbook 2011. Wellington: Ministry of Health 2011.
7. Lawrence G, Boyd I, McIntyre P, Isaacs D. Surveillance of adverse events following immunisation: Australia 2002 to 2003. *Communicable Diseases Intelligence*. 2004;28(3):324.
8. Lawrence G, Boyd I, McIntyre P, Isaacs D. Annual report: Surveillance of adverse events following immunisation in Australia, 2005. *Communicable Diseases Intelligence*. 2006;30(3):319-33.
9. Lawrence GL, Aratchige PE, Boyd I, McIntyre PB, Gold MS. Annual report on surveillance of adverse events following immunisation in Australia, 2006. *Communicable Diseases Intelligence*. 2007 Sep;31(3):269-82.
10. Lawrence G, Gold MS, Hill R, Deeks S, Glasswell A, McIntyre PB. Annual report: surveillance of adverse events following immunisation in Australia, 2007. *Communicable Diseases Intelligence*. 2008 Dec;32(4):371-87.
11. Menzies R, Mahajan D, Gold MS, Roomiani I, McIntyre P, Lawrence G. Annual report: surveillance of adverse events following immunisation in Australia, 2008. *Communicable Diseases Intelligence*. 2009 Dec;33(4):365-81.
12. Mahajan D, Roomiani I, Gold MS, Lawrence GL, McIntyre PB, Menzies RI. Annual report: surveillance of adverse events following immunisation in Australia, 2009. *Communicable Diseases Intelligence*. 2010 Sep;34(3):259-76.
13. Mahajan D, Cook J, McIntyre P, Macartney K, Menzies RI. Annual report: surveillance of adverse events following immunisation in Australia, 2010. *Communicable Diseases Intelligence*. 2011;35(4):263-80.
14. National Health and Medical Research Council. The Australian immunisation handbook. 7th edition. Canberra 2000.
15. National Health and Medical Research Council. The Australian immunisation handbook. 10th edition. Canberra 2013.
16. Gellin BG, Maibach EW, Marcuse EK. Do parents understand immunizations? A national telephone survey. *Pediatrics*. 2000;106(5):1097-102.
17. McEwan J. A History of Therapeutic Goods Regulation in Australia: Commonwealth of Australia 2007.
18. Pym M, Adams J, Booy R, Buttery J, Elia S, Elliott E, et al. The development and trial of paediatric enhanced active surveillance (PAEDS): A new surveillance mechanism for Australia. *Journal of Paediatrics & Child Health*. 2008;44(9):A16.
19. Clothier HJ, Crawford NW, Kempe A, Buttery JP. Surveillance of adverse events following immunisation: the model of SAEFVIC, Victoria. *Commun Dis Intell*. 2010;34(1):294.
20. Adverse Drug Reactions Advisory Committee. ADRAC comes to an end after 39 years. *Australian Adverse Drug Reactions Bulletin*. 2009;28(6).

21. Department of Health and Ageing. Advisory Committee on the Safety of Vaccines (ACSOV). 2013 [updated 14 August 2013; cited 2013 17 October]; Available from: <http://www.tga.gov.au/about/committees-acsov.htm>.
22. National Health and Medical Research Council. The Australian immunisation handbook. 9th edition. Canberra 2008.
23. Western Australian Department of Health. Western Australian vaccine safety surveillance. 2011 [17th June 2012]; Available from: <http://www.health.wa.gov.au/vaccination/wavss.cfm>.
24. Iskander JK, Miller ER, Chen RT. The role of the Vaccine Adverse Event Reporting system (VAERS) in monitoring vaccine safety. *Pediatric Annals*. 33(9):599-606.
25. MacDonald N, Pickering L. Canada's eight-step vaccine safety program: Vaccine literacy. *Paediatrics & child health*. 2009;14(9):605.
26. Canada. PHAo. The Canadian Adverse Events Following Immunization Surveillance System (CAEFISS). Ottawa [updated 25 January 2013; cited 2013 18 October]; Available from: <http://www.phac-aspc.gc.ca/im/vs-sv/caefiss-eng.php>.
27. Australian Government. Department of Health and Ageing. Seasonal flu vaccine and young children. April 23, 2010. Media Release [12th July 2012.]; Available from: <http://www.health.gov.au/internet/main/publishing.nsf/Content/mr-yr10-deft-dept230419.htm>.
28. Stokes B. Ministerial Review into the Public Health Response into the Adverse Events to the Seasonal Influenza Vaccine. Final Report to the Minister of Health. In: Ageing DoHa, editor. Perth: Government of Western. Australia Department of Health; 2010.
29. Horvath J. Review of the management of adverse effects associated with Panvax and Fluvax. Canberra: Australian Government Department of Health and Ageing 2011.
30. Uppsala Monitoring Centre. WHO Collaborating Centre for International Drug Monitoring. 2012 [cited 2012 9th August]; Available from: <http://www.who-umc.org/>.
31. Brown EG, Wood L, Wood S. The medical dictionary for regulatory activities (MedDRA). *Drug Safety*. 1999;20(2):109-17.
32. MedDRA. Introductory Guide MedDRA Version 14.0. 2011 [cited 2013 9 November]; Available from: http://www.meddra.org/sites/default/files/guidance/file/intguide_14_0_english.pdf.
33. The Therapeutic Goods Administration. Australian Drug Reactions System. 2012.
34. SAS statistical software. SAS Institute Inc. Version 9.3 ed. Cary, NC, USA 2005.
35. Australian Bureau of Statistics. Australian Demographic Statistics, Dec 2011. Canberra 2012 [updated 20 June 2012; cited 2012 17 September]; Available from: <http://www.abs.gov.au/AUSSTATS/abs@.nsf/DetailsPage/3101.0Dec%202011?OpenDocument>.
36. Jacobson RM, Adegbenro A, Pankratz VS, Poland GA. Adverse events and vaccination-the lack of power and predictability of infrequent events in pre-licensure study. *Vaccine*. 2001;19(17-19):2428-33.
37. Armstrong P, Dowse G, Effler P, Carcione D, Blyth C, Richmond P, et al. Epidemiological study of severe febrile reactions in young children in Western Australia caused by a 2010 trivalent inactivated influenza vaccine. *BMJ open*. 2011;1(1).
38. Goldman SA. Limitations and strengths of spontaneous reports data. *Clinical therapeutics*. 1998;20:C40-C4.
39. Chaves SS, Haber P, Walton K, Wise RP, Izurieta HS, Schmid SD, et al. Safety of Varicella Vaccine after Licensure in the United States: Experience from Reports to the Vaccine Adverse Event Reporting System, 1995-2005. *Journal of Infectious Diseases*. 2008;197 Supplement(2):S170-S7.
40. Slade B, Leidel B, Vellozzi C, Woo EJ, Hua W, Sutherland A, et al. Postlicensure Safety Surveillance for Quadrivalent Human Papillomavirus Recombinant Vaccine. *JAMA*. 2009;302(7):750-7.
41. Wise R, Iskander J, Pratt RD, Campbell S, Ball RM, Pless RP, et al. Postlicensure Safety Surveillance for 7-Valent Pneumococcal Conjugate Vaccine. *JAMA*. 2004;292(14):1702-10.

42. Hull B, McIntyre P, Heath T, Sayer G. Measuring immunisation coverage in Australia. A review of the Australian Childhood Immunisation Register. *Australian Family Physician*. 1999;28(1):55.
43. Hull B, Dey A, Mahajan D, Menzies R, McIntyre PB. Immunisation coverage annual report, 2009. *Commun Dis Intell*. 2011;35(2):132-48.
44. Hull BP, McIntyre PB. A re-evaluation of immunisation coverage estimates from the Australian Childhood Immunisation Register. *Communicable Diseases Intelligence*. 2000;24(6):161-5.
45. Van Lier A, Oomen P, de Hoogh P, Drijfhout I, Elsinghorst B, Kemmeren J, et al. Præventis, the immunisation register of the Netherlands: a tool to evaluate the National Immunisation Programme. *Eurosurveillance*. 2012 26 April 2012;17(17):33.
46. Buttery J, Danchin M, Lee K, Carlin J, McIntyre P, Elliott E, et al. Intussusception following rotavirus vaccine administration: post-marketing surveillance in the National Immunization Program in Australia. *Vaccine*. 2011;29(16):3061-6.
47. Miller M, Turner N. Suggestions for improving the monitoring of adverse events following immunization in New Zealand. *The New Zealand medical journal*. 2002;115(1162):U186.
48. Department of Health and Ageing Therapeutic Goods Administration. About the Database of Adverse Event Notifications. 2012 [updated 28 August 2012; cited 2012 5 September]; Available from: <http://www.tga.gov.au/safety/daen-about.htm>.

Chapter 4

Measles in Australia: on the path to elimination

“As a parent, I know we all want to protect our children so no mother or father loses a child from measles...Together, let’s make measles history.”

– Kofi Annan

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Abbreviations & Acronyms

| | |
|-------|--|
| ACIR | Australian Childhood Immunisation Register |
| ACT | Australian Capital Territory |
| CDC | Centers for Disease Control |
| CFT | Complement Fixation Test |
| DoHA | Department of Health and Ageing |
| ED | Emergency Department |
| ELISA | Enzyme-linked Immunosorbent Assay |
| GP | General Practice |
| HAPS | Hunter Area Pathology Service |
| ICPMR | Institute for Clinical Pathology and Medical Research |
| IF | Immunofluorescence |
| IgG | Immunoglobulin G |
| IgM | Immunoglobulin M |
| IQR | Interquartile Range |
| LHD | Local Health District |
| MAE | Master of Philosophy (Applied Epidemiology) |
| MCC | Measles Control Campaign |
| MM | Measles Mumps Vaccine |
| MMR | Measles Mumps Rubella Vaccine |
| MMRV | Measles Mumps Rubella Varicella Vaccine |
| MoH | Ministry of Health |
| MRN | Medical Record Number |
| NCIRS | National Centre for Immunisation Research and Surveillance |
| NHIG | Normal Human Immunoglobulin |
| NHMRC | National Health and Medical Research Centre |
| NIP | National Immunisation Program |
| NNDSS | National Notifiable Disease Surveillance System |
| NSW | New South Wales |
| NT | Northern Territory |
| PCR | Polymerase Chain Reaction |
| PEP | Post-exposure Prophylaxis |
| PHU | Public Health Unit |
| QLD | Queensland |
| SA | South Australia |

| | |
|--------|---|
| SAGE | Strategic Advisory Group of Experts on Immunisation |
| SAS | Statistical Analysis System |
| SEALS | Sydney Eastern Area Laboratory Service |
| SLAM | Signalling Lymphocyte-activation Molecule |
| SSPE | Subacute Sclerosing Panencephalitis |
| SSWLHD | Sydney South West Local Health District |
| TAS | Tasmania |
| VIDRL | Victorian Infectious Diseases Reference Laboratory |
| UNICEF | United Nations Children's Fund |
| US | United States |
| USD | United States Dollar |
| VIC | Victoria |
| VIDRL | Victorian Infectious Disease Reference Laboratory |
| WA | Western Australia |
| WHA | World Health Assembly |
| WHO | World Health Organization |
| WPRO | Western Pacific Regional Office |
| WSLHD | Western Sydney Local Health District |

Preface

During my MAE, my work on measles related projects has led somewhat to a fascination to measles; a disease so infectious it has been described by Professor Peter McIntyre as a 'heat-seeking missile'— finding those most susceptible and infecting them. Such is the ferocity of the virus, that it has been attributed to nearly wiping out entire Indigenous populations.¹ A disease that, prior to the availability of a vaccine killed an estimated 2.6 million individuals per year.² Since the development of a highly effective vaccine, the burden of measles has reduced considerably.³ To such an extent that in 2012, a Measles & Rubella Initiative was developed. By 2015, a target date for measles eradication would be given; through focusing on achieving high two-dose vaccination coverage and establishing high quality surveillance systems.⁴ Most recently, South-East Asia has committed 2020 as the year for measles elimination in the region, the final WHO Region to announce a set target date for measles elimination.⁵

Although measles elimination has not officially been declared in Australia, a number of indicators used to declare measles elimination were met which were used by a group of measles experts to justify measles elimination in Australia.⁶ During the first year of my MAE, however, a large measles outbreak occurred in NSW. This outbreak has the potential to jeopardise the elimination status in the country.

It was the vision of outbreak investigations, particularly conducting 'shoe-leather' epidemiology that led me to apply for the MAE program. I envisaged that investigating outbreaks would equip me with a range of new and varied skills whilst contributing to timely public health action. And indeed, participating in control measures for the largest national measles outbreak in Australia in 2012 enabled me to be involved in a number of activities and learn a number of skills. It was a highly rewarding period of my MAE and the major highlight was getting to work with a multidisciplinary team, including epidemiologists, public health nurses, infectious disease consultants, laboratory scientists and emergency department clinical staff.

Although the National Centre for Immunisation Research and Surveillance (NCIRS) is not responsible for outbreak investigation, the close relationship with the Western Sydney Local Health District (WSLHD) enabled Alexis (my fellow MAE at NCIRS) and I to be involved in the measles outbreak, through the generosity of the manager of the

Communicable Diseases and Immunisation branch, Dr Vicky Sheppeard. During the peak of the measles outbreak, we were given the opportunity to also work at the South Western Sydney and Sydney Local Health District (SSWLHD) and the NSW Ministry of Health (MoH). The measles outbreak also gave Alexis and I the opportunity to present our analysis to infectious disease specialists at the Children's Hospital Westmead infectious disease grand rounds and to colleagues at NCIRS through journal club.

Interestingly, at the time of the measles outbreak, I was fortunate to become a member of the National Measles Elimination Working Group. One of my first responsibilities was to conduct a literature review on measles epidemiology over the past decade in Australia. The collation of literature enabled the Working Group to review what research has been conducted in Australia and facilitate the introduction and discussion sections of anticipated publications proposed by the Working Group. It also served me well, through expanding my knowledge of measles in Australia, which was important given the number of measles-related projects that I would be conducting as part of my MAE.

Through my MAE measles related projects I have been involved in a number of diverse public health activities and research focussed on measles. These included:

1. Contact tracing individuals exposed to a measles infectious case;
2. Answering measles-related questions from individuals presenting to a measles post-exposure prophylaxis clinic;
3. Examining medical charts and building maps to identify the source of a cluster of measles in a hospital emergency department;
4. Conducting data analysis on infant measles cases for the NSW extraordinary measles expert group;
5. Creating a line lists;
6. Entering data into excel spread sheets of measles contacts
7. Developing a questionnaire to identify the source of measles transmission in a paediatric hospital;
8. Interviewing suspected sources of measles transmission in a paediatric hospital;
9. Hypothesising the transmission of measles between two cases in an emergency department;

10. Investigating cross-over times in health-care settings during the measles outbreak
11. Conducting a literature review on measles epidemiology in Australia;
12. Understanding the biases in using laboratory data to calculate a non-measles discard rate in New South Wales;
13. Analysing and interpreting measles notification and hospitalisation data;
14. Learning about the biases associated with notification and hospitalisation data;
15. Applying infectious disease models using notification data to estimate the reproduction number of measles;
16. Cleaning multiple datasets extracted from laboratories to calculate a non-measles discard rate in New South Wales;
17. Contributing epidemiological evidence of Australia's elimination status as a member of the measles elimination working group;
18. Learning what criteria is necessary for the verification of measles elimination;
19. Learning to develop a poster for a national conference; and
20. Preparing and presenting a research project at an international conference;

Structure of this chapter

This chapter encompasses reports on all the measles-related projects that I was involved in as part of my MAE. Section A includes an overall introduction to measles and a literature review of measles epidemiology in Australia. Section B comprises of an epidemiological review of measles between 2000 and 2011. Notification data, hospitalisation data and death data were analysed to provide an overview of the burden of measles in Australia. Section C incorporates the estimation of a measles reproduction number using notification data; firstly to assess Australia's measles elimination status and secondly, to evaluate the methodology of estimating R , particularly in the context of lower-income countries. Section D includes the calculation of a measles discard rate using laboratory data in New South Wales (NSW) to examine the quality of surveillance in the state. Section E incorporates two projects that were conducted during a measles outbreak in NSW during 2012. The first component of this section outlines the challenges in identifying a source measles case in a paediatric ED setting using a non-validated algorithm and the second component provides a review of the epidemiology on healthcare transmissions that occurred during the outbreak.

SECTION A

An Introduction to Measles

Introduction

Measles is a single-stranded ribonucleic acid (RNA) virus that is a member of Paramyxoviridae family. The Paramyxoviridae family are an important human pathogen, commonly causing respiratory disease among infants and children (respiratory syncytial virus, parainfluenza) and mumps.⁷ Humans are the only known natural reservoir for measles.⁸

Clinical presentation

Initially, infection is characterised by fever, rhinitis, coughing, conjunctivitis and Koplik spots (prodromal phase).⁸ Koplik spots usually occur prior to rash onset and are identified as small, bluish-white lesions on the buccal mucosa.⁸ The rash begins on the face and behind the ears and progressively spreads to the torso, and then down to the extremities. The rash is characteristically maculopapular and erythematous. It develops due to an interaction between immune T cells and virus-infected cells⁷ and in some instances, may not occur in immunocompromised individuals.⁹ Recovery occurs shortly after rash onset.⁹

Although in most cases, measles is self-limiting, complications can occur, and even result in death. Complications have been reported to occur in up to 40% of reported cases, the risk highest in the very young and malnourished.⁸ Complications include otitis media, diarrhoea, pneumonia and encephalitis.^{8, 10, 11} Pneumonia is the most common complication of measles that causes death¹⁰. A rare but extremely serious neurological complication is sub-sclerosing panencephalitis (SSPE); a degenerative condition that results in persistent and prolonged infection of defective measles virus in the central nervous system and in most cases leads to death.^{8, 10}

Pathogenesis

Measles is one of the most infectious human diseases known to humankind with the route of transmission via the upper respiratory tract.⁸ The incubation period is usually 7–18 days, from exposure by an infectious case to the onset of symptoms.¹² However, an incubation period of 23 days has previously been reported.¹³

Diagnosis

In the past, measles was often diagnosed by clinical signs and symptoms; however, as measles becomes rarer, challenges in clinical diagnosis exist. Previous studies have highlighted this through the low positive predictive value of a clinical case definition for measles.^{14, 15} Clinicians working in places where measles is rare, may never have witnessed a case of measles in their career, resulting in inexperience and perhaps low suspicion when a true measles case presents. Additionally, a myriad of other diseases and conditions may present with similar signs and symptoms to measles, making clinical diagnosis even more challenging.¹⁶

Serology

The most common diagnosis method for acute infection is serology testing to detect measles immunoglobulin M (IgM) antibodies. IgM are detectable from rash onset for 6–8 weeks.¹⁷ Enzyme-linked immunoassay (ELISA) is the most common way to test for antibodies. Immunoglobulin G (IgG) antibodies are also produced during rash onset however form more slowly and are detectable for a lifetime.¹⁷ ELISA, haemagglutination inhibition (HI), indirect immunofluorescence (IF), complement fixation testing (CFT) can be used to test for IgG antibodies.^{18, 19} A four-fold rise titre of IgG antibody in two serum samples taken at least ten days apart indicates acute infection; except if an individual was vaccinated with a measles containing vaccine eight days to six weeks prior.²⁰ The test sensitivity for IgM by ELISA varies by disease progression, at four days after rash onset IgM test sensitivity is less than 50%, however, increases to 88–100% one to three weeks after rash onset.²¹ The specificity of the test varies between 60–97%.²¹

Culture

Virus isolation in culture is not routinely used as a diagnosis method for measles as sensitivity is lower than serological methods,²⁰ however it is useful for molecular epidemiologic surveillance.¹⁸ Culture of measles virus from the Vero SLAM (signalling lymphocyte-activation molecule) cell line is currently recommended by the World Health Organization (WHO) laboratory network.²⁰

Antigen detection

Measles antigen detection by direct and indirect IF is a technique that can rapidly diagnose measles. Nasopharyngeal aspirates and respiratory secretions can be used

as specimens and are stained with monoclonal antibodies directed against structural proteins of the virus. The sensitivity is approximately 50–60% and the specificity is not known, but around 90–95% has been reported.²¹

RNA detection by PCR

Rapid diagnosis can also occur through Polymerase Chain Reaction (PCR). Suitable specimens include respiratory secretions, early catch urine, sera, cerebrospinal fluid and throat secretions. Both the test sensitivity and specificity are high, approaching 100%.²¹

Measles vaccine

In 1954, Edward and Peebles isolated measles virus in tissue culture.¹⁷ Not long after, the attenuated Edmonston B vaccine was developed and first licensed in 1963 in the United States (US).¹⁷ Since then, a number of vaccines derived from the Edmonston strain have been further attenuated. In 1971, a combined live vaccine that included attenuated mumps, measles and rubella virus was licensed in the US.¹⁸ The combined measles-mumps-rubella (MMR) vaccine has been used in Australia for many years; however, more recently, the measles-mumps-rubella-varicella (MMRV) vaccine has become available.²² There are currently four vaccines licensed in Australia that contain a measles component (two MMR and two MMRV). M-M-R II (MMR) and ProQuad (MMRV) use Enders' attenuated Edmonston strain for measles whilst Priorix (MMR) and Priorix-tetra (MMRV) use the Schwarz strain for measles.²³

Vaccine efficacy

Measles containing vaccine induces both humoral and cellular immunity.¹⁷ Although long-term immunity occurs in most individuals who receive one dose of measles-containing vaccine, approximately 5% will not respond.²² A second dose of vaccine in these non-responders however, will produce an almost complete response²⁴ with 99% of individuals having sufficient antibody levels to protect against the disease after two doses.²²

There has been much debate on the optimum time to initiate vaccination against measles. It has been well-documented that vaccine-derived maternal antibodies wane at a faster rate than naturally derived maternal antibodies in infants.²⁵ However, it has come to light that naturally derived maternal antibodies in infants also wane at a rate

fast enough to lose protection by six months of age.²⁶ Vaccination too soon, however, may interfere with existing passive antibodies resulting in vaccine failure.¹⁷ The age to begin vaccination requires assessing the age of the highest rate of seroconversion and the risk of acquiring disease before this age.⁸ Current recommendations range from 6–15 months of age.⁸ One study comparing the humoral immune response in six-, nine- and 12-month old infants found significantly higher seroconversion in 12-month old infants compared to six-month old infants following receipt of measles vaccine.²⁷ In contrast, cell-mediated immunity was similar in these age groups regardless of the presence of maternal antibodies prior to vaccination.²⁸

A review of 70 vaccine effectiveness studies published between 1960 and 2010 identified that vaccine effectiveness for one dose of vaccine was 92 % (interquartile range [IQR]; 86%–96%) when administered to children ≥ 12 months compared to 77.0% (IQR; 62%–91%) in children administered with vaccine at 9–11 months.²⁹ The high effectiveness of the vaccine was further supported in a Cochrane review which concluded that one-dose of measles vaccine was $\geq 95\%$ effective in protecting against measles.³⁰ A more recent study identified that the vaccine effectiveness of one dose of measles vaccine was 95.9% (95% CI; 87.4%–98.7%). Interestingly, vaccine effectiveness was greater in two-dose recipients when the first-dose was administered at ≥ 15 months compared to 12–14 months (97.5% versus 93.0%).³¹

A history of measles

Measles virus is believed to be a descendent of rinderpest virus and/or the modern canine distemper during the Epipalaeolithic Age, a period when humans began domesticating cattle and dogs in the Middle East.³² It is believed that humans became a host to measles around 4000 BC, spreading the virus as civilisations evolved.³² Measles was established during 3000 BC in civilisations of the Tigris-Euphrates valley.¹ From there, the disease gradually spread to other civilisations including Indus, Egyptian and Ganges.³²

By the Middle Ages, measles became established in China, Japan, the Middle East, North Africa and Europe.³² During this period, Abu Bakr Muhammad Ibn Zakariya al-Riza, a Persian physician noted for being “one of the greatest physicians Islam ever produced”³³ provided the first written account of measles¹. In 910, in his *Treatise on*

Smallpox and Measles, he was credited as the first to clearly differentiate between measles and smallpox.^{32, 33}

During the sixteenth century, it is believed that European explorers took measles to the New World where numerous epidemics occurred. As emigration occurred in America, measles epidemics followed. One epidemic in 1837 had particularly dire consequences— a 98% mortality rate resulting in the near extinction of the Mayan Indian tribe.¹

Measles history in Australia

Pre-vaccine era

It is understood that measles did not arrive to Australia until 1850.³⁴ Prior to this, restrictions on the immigration of families with children, smaller ships and a longer journey from Britain to Australia were likely to have prevented measles from appearing in Australia any earlier.³⁴ Indeed, William Charles Wentworth, a prominent Australian explorer who lived in colonial NSW in 1824 noted that *"infantile diseases are almost unknown; the measles, whooping cough, and smallpox being entirely so"*.³⁵ The first recorded case of measles in Australia was in 1850 in Victoria, following the voyage of the ship the 'Persian' from Britain. Infectious measles cases disembarked in Victoria (VIC) and subsequently spread the disease to others. From there, as Australia's population grew, so did measles cases. The first recorded deaths due to measles occurred in 1857 in Queensland (QLD). Prior to 1900, measles epidemics appeared to have been contained within states and territories, occurring at different periods. It was only post-1900 that interstate transmission of measles commenced, observed by epidemics that occurred simultaneously in a number of jurisdictions. Mortality was greatest in children aged <5 years (50–80% of all deaths) followed by children aged 5–15 years (5–20%).³⁵

Severe epidemics appeared to end within 12 months and would be separated by inter-epidemic periods where mortality rates dropped to zero.³⁵ Biennial epidemics were observed, once the accumulation of susceptible populations was large enough to perpetuate an outbreak. Such observations also were observed in the United Kingdom and the US during the pre-vaccine period.^{18, 36}

In 1909, South Australia (SA) became the first state to make the notification of measles mandatory.³⁵ Fluctuations in disease were observed during this period with a peak in 1925 with 14,804 notifications (2742 notifications per 100,000 population) reported.³⁷ In 1929, the Federal Capital Territory (Australian Capital Territory) made measles notifiable, and were followed by Northern Australia (Northern Territory, 1931) and Western Australia (1940).³⁷

The vaccine era

In 1968, a live, attenuated measles vaccine became available in Australia (**Table A-1**).³⁸ The following year, vaccination was recommended for children 12–23 months of age and by 1972, all states and territories subsequently funded measles vaccination for these age groups.³⁹ After the introduction of measles vaccination, rates of measles drastically decreased to 1.4 notifications per 100,000 population in 1989. In 1991, the National Notifiable Disease Surveillance System (NNDSS) was established, resulting in the national collation, analyses and reporting of notifiable diseases, including measles.⁴⁰

Table A-1. A history of measles containing vaccine policy in Australia^{38, 39}

| Year | Intervention |
|------|---|
| 1968 | Live attenuated measles vaccine registered |
| 1971 | Vaccine funded in children 12–23 months in all jurisdiction except NSW |
| 1972 | Vaccine funded in children 12–23 months in all jurisdiction in NSW |
| 1975 | Measles included in Australia's first immunisation schedule for infants 12 months of age |
| 1982 | Vaccine replaced by measles-mumps (MM) vaccine |
| 1989 | MM vaccine replaced by measles-mumps-rubella (MMR) vaccine |
| 1992 | NHMRC recommended second dose |
| 1993 | Second dose of MMR funded for children 10–16 years of age |
| 1998 | Measles Control Campaign commenced Second dose of MMR vaccine lowered to children 4–5 years old. |
| 2000 | Second dose of MMR vaccine condensed to children 4 years old. |
| 2001 | Young adult campaign funded |
| 2013 | Second dose of MMR vaccine replaced by MMRV and lowered to children 18 months old. |

Global measles elimination and the feasibility of eradication

Since the development of an effective vaccine, there has been much discussion on the prospect of measles eradication.⁴¹ By the early 1980s, nearly all Member States of the WHO had included at least one dose of measles vaccine in their routine childhood immunisation and coverage increased to around 80% by 2000.⁴² Subsequently, the number of measles cases declined between 1983 and 2000, although, variation between and within WHO regions was noted.⁴² By 1994, the Region of the Americas had established 2000 as the target year of elimination. In 1997, the Eastern Mediterranean Region was the second region to set an elimination target year (2010) followed by the European Region (2012).⁴³

In 2000, a technical working group reviewed the current status of measles globally, and concluded that supplementary and routine immunisation activities should occur to provide a second opportunity to vaccine children who may have missed out on receipt of the first dose of vaccine or failed to seroconvert from the first dose.⁴⁴ During the same year, the US reported the elimination of endemic measles.⁴⁵

A year later, the Measles Initiative was launched; it is a global partnership between the American Red Cross, the United Nations Foundation, the US Centers for Disease Control and Prevention (CDC), United Nations Children's Fund (UNICEF) and the WHO. Technical and financial support is provided to national governments to increase and sustain population immunity through: routine immunisation and campaigns; monitoring measles through surveillance and; identifying and managing disease outbreaks.⁴

By 2002, the Region of the Americas had declared elimination; being the first and at present, the only WHO Region to have achieved and sustained measles elimination⁴⁶. The Western Pacific Region, of which Australia is a part of, set 2012 as the target year for measles elimination.⁴⁷ Progress has been made towards establishing elimination in the region; however increasing the first and second dose of measles vaccine coverage in some countries is still required, in addition to introducing a booster dose to the vaccine schedule in Lao People's Democratic Republic, Vietnam, Solomon Islands and Papua New Guinea.⁴⁸

Based on the success in the Region of the Americas, the biological and technical feasibility of measles eradication was acknowledged by the Global Consultation of the Feasibility of Measles Eradication advisory panel in 2010.⁴⁹ However, a set target date is yet to be made pending review of regional measles control and elimination targets for 2015.²

The will to eradicate measles garnered further support through the endorsement of the Global Vaccine Action Plan by the World Health Assembly (WHA) in 2012. The framework reiterates the goal of eliminating measles in at least 4 WHO Regions by 2015, and as an indicator, will be reviewed in 2013 at the WHA.⁵⁰ To monitor the progress towards measles elimination, a working group on measles and rubella as part of the Strategic Advisory Group of Experts on Immunisation (SAGE) developed a guide for Member States.⁵¹ This was endorsed by SAGE at the end of 2012.⁵¹

Having reviewed the literature on the history of measles, its introduction into Australia and the global will to eradicate measles, I conducted a more focussed literature review on measles epidemiology in Australia over the last two decades– highlighting a period where the country transitioned from measles control to measles elimination. This literature review was suggested by the National Measles Elimination Working Group and also would enhance my understanding of measles given the numerous measles-related projects I would be involved in. The literature review is structured to be in chronological order to highlight the impact of changes in vaccine policy on the epidemiology of measles.

A literature review on measles epidemiology in Australia over the past two decades

Research question

What changes in measles epidemiology have occurred over the last two decades in Australia?

Search methods

Medline and Informit were used to search for publications and a backward citation search used Web of Science. A total of 4050 measles publications and 42,140 publications with search term 'Australia' were captured between 1992 and 2012. Seventy-one articles with both 'measles' and 'Australia' were found and all abstracts were reviewed (**Table A-2**). Forty-five abstracts were deemed useful in contributing to addressing the literature research question.

Table A-2. Results of the literature search using Medline

| Search terms | Number of records |
|--|-------------------|
| Measles | 4050 |
| Australia | 42140 |
| Measles AND Australia | 71 |
| Measles AND Australia, between 1993 and 2012 | 71 |

Published NNDSS Annual Reports were also accessed through the Department of Health and Ageing (DoHA) website.

Literature review results

The 1990s

Since 1993, the incidence of measles in Australia has reduced considerably. Between 1993 and 1998, there were over 12,000 cases of measles notified nationally (notification rate= 11.4 per 100,000 population),⁵² the majority occurring in 1993 and 1994 (approximately 10,000 cases).⁵² Community transmission appeared to be the main setting for transmission during this period. Between 1993 and 1994 there were a number of large outbreaks that occurred around the country. In one large outbreak during June to December 1993, 889 notifications occurred in just one region of

metropolitan Sydney (western Sydney), primarily affecting the 0–14 year age-group. A case-ascertainment study during this outbreak, suggested that the notification system captured less than half of all cases, indicating the poor sensitivity of the notification system during this period.⁵³ In 1993 and 1994, the Northern Territory (NT) was the jurisdiction with the highest rates of measles.⁵² During a 1994 outbreak in Alice Springs, 55% of 259 cases in a remote community were Aboriginal.⁵⁴ The attack rate among Aboriginal individuals was estimated to be 12.6 per 1000 population, much higher than attack rates observed in non-Aboriginal individuals (4.0 per 1000 population).⁵⁴ School-based transmission was also found to be an important setting for transmission during a 1994 outbreak in Western Australia (WA) affecting 53 individuals, a large proportion from a high-school.⁵⁵

Consequent to the large outbreaks experienced in 1993 and 1994, a second dose of MMR vaccine was introduced in 1994; targeting children aged 10–16 years.³⁸ By 1995, measles notification rates reduced to 7.3 per 100,000 population compared to 25.7 per 100,000 population in 1994.⁵⁶ In 1996, the reduction in notification rate (2.7 per 100,000 population) was even more marked.⁵⁷

A significant factor in shifting the focus from measles control to measles elimination, was the commencement of the Measles Control Campaign (MCC) in 1998. The MCC was part of the 'Immunise Australia: Seven Point Plan'; evidence that Australia was committed to eliminating measles in the country.⁵⁸ The MCC included: ⁵⁹ reducing the age of the second dose of MMR to four to five years; a school-based mass vaccination program of children aged 5–12 years (July–December), regardless of vaccination status; encouraging participation in the campaign through media and education programs; distributing letters to parents of preschool and high-school aged children to encourage vaccination and; providing financial incentives to parents and general practitioners for vaccination.

Following the implementation of the MCC, the measles notification rate reduced in 1999, to the lowest rate since the inception of the NNDSS (1.2 per 100,000 population).⁶⁰ However, it was during 1999 that healthcare workers were identified as a susceptible population.⁶¹ In a Victorian outbreak, six of the 75 cases were healthcare workers.⁶¹ This outbreak also highlighted young adults as a susceptible group, with 85% of cases aged 18–31 years. Community and healthcare facilities were identified

as important settings for measles transmission during this outbreak.⁶¹ The impact of the MCC however was apparent, with a national serological survey indicating immunity had increased from 85% (pre-MCC campaign) to 90% after the campaign (January–May 1999), with the greatest increase in pre-school and primary school children.⁶² Further evidence of the success of the MCC was evident through mathematical modelling, which estimated that the reproduction number for measles reduced from 0.90 pre-campaign to 0.57 post-campaign.⁶³

With further reductions in measles cases, and evidence of a successful MCC in increasing immunity against measles, it seemed the shift from measles control to the goal of elimination was in the horizon. An important indicator to assess whether an endemic circulating measles virus exists is through genotyping. Between 1973 and 1998, 35 wild type viruses were circulating Australia. During 1999, a novel genotype G3 was identified in Queensland which was traced to a refugee population from East Timor.^{64, 65}

To this point, it is clear that measles notifications have declined, however, it was also important to establish the burden of measles through hospitalisations and deaths during the 1990s, particularly in the context of changes to the vaccine program. Between 1993 and 1998, there were 1856 hospitalisations where measles was recorded as the principal diagnosis (hospitalisation rate 2.1 per 100,000 population).⁵² The most common complication reported was pneumonia (7%) and otitis media (3%). Children 0–4 years of age had the highest notification rate (11.6 per 100,000 population) followed by children aged five to 14 years (4.2 per 100,000 population). Seven deaths associated with measles infection were reported between 1993 and 1997.⁵²

Assessing vaccine uptake is a useful tool to determine if there is a relationship between uptake and the number of cases. Coverage for the primary dose of MMR (MMR1), assessed at 24 months by three-month cohorts between January and December 1998, was less than 95% in all jurisdictions; with only Queensland reaching greater than 90% coverage. However, underestimates of coverage have been claimed, estimated to be approximately five per cent.⁵²

The 2000s

Like the year 1999, the notification rate in 2000 reduced even further (0.6 per 100,000 population).⁶⁶ During this year, however, the susceptibility of healthcare workers was again identified, when two ambulance officers became infected with measles following exposure to an infectious case.⁶⁷ During a cluster of measles in Queensland, cases presented multiple times to a number of healthcare facilities whilst infectious.⁶⁸ With low suspicion of measles among clinicians and no vaccine policies implemented for healthcare workers at the time, it was postulated⁶⁸ that healthcare facilities propagated measles outbreaks. This was further supported by a general practice (GP) surgery waiting room in NSW being the setting of transmission of a cluster in 2000, involving five cases of measles.⁶⁹

Measles notification rates had again reduced in 2001–2002, to 0.4 per 100,000 population.⁷⁰ A large proportion of cases during this period occurred in the 15–24 year age group. Young adults once more were affected by measles, the median age of a 2001 Victorian outbreak of 51 cases was 25 years (range= 10 months–34 years).⁷¹ Another characteristic of this outbreak was the lack of suspicion of measles by clinicians leading to multiple presentations. A total of 62 presentations to a healthcare facility occurred in the 22 hospitalised cases, with measles suspected during the first presentation in only 13% of hospitalised cases.⁷¹ Of great concern however, was that young adults were susceptible to acquiring measles. Young adults were too old to have been eligible for the second dose of MMR when it was included in the vaccine schedule, and lacked natural immunity, as measles incidence had become rare during their childhood.⁷² To combat the gap in immunity among young adults, the Commonwealth Government provided funding for MMR vaccine in adults aged 18–30 years in 2001 and 2002.⁵⁸ Vaccination was rolled-out through GPs, hospital emergency departments (ED) and other healthcare facilities in the Young Adult Campaign. A serosurvey conducted in Victoria before and after the campaign; however, found no significant difference in serological immunity between the two time periods⁷³ suggesting the campaign had been unsuccessful. The failure of the Young Adult Measles Campaign was further confirmed during two 2003 outbreaks in Adelaide where the median age was 23 years (range= 9 months– 36 years)⁷⁴ and in NSW where the median age was 24 years (range= 2 months–38 years).⁷⁵

Despite young adults remaining a susceptible population, further reduction in measles notifications was providing more evidence of Australia's progress towards measles elimination. In 2003 to 2004, there were 92 and 54 cases of measles in Australia, respectively. A decrease in notification rate from 0.5 per 100,000 population in 2003 to 0.2 cases per 100 000 population in 2004.⁷⁶ By 2005, measles became even rarer, with only ten cases of measles nationally; the lowest rates of notifications (< 0.1 per 100,000 population) since the NNDSS was established.⁷⁷ The progress towards eliminating measles was, however, disrupted in 2006. An increase in measles cases occurred with 125 cases notified and a notification rate of 0.6 per 100,000 population.⁷⁸ Eighty-two cases were part of a multi-state outbreak during a tour of a spiritual leader from India.⁷⁹ The rise in cases was short-lived however, and in 2007, only 12 cases (0.1 per 100,000 population) were reported, of which seven were acquired overseas.⁸⁰

As expected, with declining measles notifications, a reduction in hospitalisations also occurred. Between July 1998 and December 2000, there were 111 measles hospitalisations with measles as the principal diagnosis.⁸¹ The rate of hospitalisation was 0.3 per 100,000 population compared to 2.1 per 100 000 population in July 1993–June 1998. The highest rate occurred in children 0–4 years old and the median length of stay was highest in the 15–24 year and 25–59 year age groups (both four days). No deaths were recorded during this period. Pneumonia was the most common complication among all measles hospitalisations (eight per cent) followed by neurological complications (five per cent).⁸¹

A decline in measles hospitalisations again occurred during July 2001–June 2002 compared to July 1998–December 2000. There were 96 hospitalisations with measles as a principal diagnosis and rate 0.20 per 100,000 population⁷⁰ compared to a rate of 0.3 per 100,000 population in July 1998–December 2000). The most common complication for all measles hospitalisations was pneumonia (7%). Similarly, no deaths were recorded during this period.⁷⁰ As outlined above, molecular epidemiological evidence is important to determine whether an endemic strain of measles exists. During 1999–2001, there was again no evidence of a circulating genotype; nine different genotypes were identified including one new genotype (D9).⁸²

Between July 2003 and June 2005, there were 72 hospitalisations with a hospitalisation rate of 0.12 per 100,000 population where measles was the principal diagnosis

compared to 0.2 per 100,000 population (hospitalisation rate=0.12 per 100,000 population) in July 2001–June 2002.⁸³ The hospitalisation rate was greatest in the 0–4 year age group (0.76 per 100,000 population) between July 2003 and June 2005, however, the median length of stay was greatest in the 25–59 year age group (three days) where measles was the principal diagnosis.⁸³ No deaths were recorded during this period, however, there was one death in 2004 associated with SSPE.⁸³ The following year, another case of SSPE occurred resulting in three hospital admissions.⁸⁴ Of all hospitalisations coded with measles, six per cent were recorded to have pneumonia and 13% were recorded as experiencing other complications.⁸³

Despite the increase in notifications in 2006, the rate of hospitalisations remained low, with 52 hospitalisations (rate= 0.13 per 100 000 population) in July 2005–June 2007. Similar to previous years, rates were highest in the 0–4 year age group (0.54 per 100,000 population), however, length of stay was highest in individuals over five years of age (median=two years). Nine hospital separations were coded as experiencing complications, of which five were due to pneumonia. No deaths associated with measles were recorded during this period.⁸⁵

Although young adults were continuously identified as a susceptible population and thus jeopardising Australia's target for elimination, one area of improvement was the increase in measles vaccine coverage. Only Queensland exceeded 90% coverage of MMR1 by two years of age in previous coverage estimates (31 March 1998–31 December 1998). In comparison, vaccine uptake of MMR1 at two years of age, measured between 31 March 1999 and 30 September 2001 was approximately 93% and remained stable during this period. South Australia was the only jurisdiction to reach the target of 95% coverage.⁷⁰ The booster dose of MMR (MMR2) uptake measured at six years of age identified that coverage was lower, at around 82%, with little change occurring between 31 March 1999 and 30 September 2001.⁷⁰ No comparisons were able to be made with previous years as data on vaccine coverage of 4–5 years born since the ACIR commenced would only be four years of age in 2000.⁸¹ There was little change in coverage during 2001–2003, remaining at around 93% for MMR1 at 24 months and just below 85% for MMR2 at six years.⁷⁰ MMR1 coverage between 2003 and 2005 at 24 months of age was between 93% and 95% and remained steady during this period, similar to coverage of approximately 93% during

2001–2003. Likewise, MMR2 coverage at six years between 2003 and 2005 remained around 85% with little change during the same period in 2001–2003.⁸³

Given the number of healthcare workers infected by measles in previous outbreaks as outlined above, it was important to recognise the need for healthcare workers to be protected against measles— particularly as an occupation health and safety issue. Each state and territory has their own policy and recommendations. In NSW, a policy directive was implemented in 2007, requiring mandatory immunisation of all NSW Health staff against a number of vaccine preventable diseases, including measles.⁸⁶ Current Australian guidelines, recommend that all new staff should be assessed and offered vaccination for testing for certain diseases (including measles) prior to working in high-risk areas.⁸⁷

Furthermore, coverage among children was improving. In 2007, MMR1 coverage rose to 94% nationally at 24 months of age with the 95% target coverage reached in Tasmania and the NT. MMR2 coverage at six years remained lower at 88%, Victoria was the only jurisdiction to achieve uptake greater than 90% (91%) however increased, compared to previous years.⁸⁸

The era of measles elimination

In 2008, a group of measles experts argued that measles had been eliminated in Australia since 2005, in the form of a publication.⁶ A number of indicators were used to argue the case of elimination; based on indicators developed by the Western Pacific Regional Office (WPRO) of the WHO that aimed to assist countries in implementing a national plan for measles elimination.⁸⁹ One of the indicators was a low incidence of measles (< 1 case per million population)⁶ which in 2008, was not reached. During 2008, 65 cases of measles were reported (0.3 per 100,000 population) of which 26% were reported as acquired overseas. Further progress however, was made in increasing vaccine coverage. In 2008, MMR1 national coverage remained stable at 94%, with the Australian Capital Territory (ACT) and the NT the only jurisdictions to exceed the target uptake of 95%.⁹⁰ During this year, the assessment age for MMR2 coverage was reduced to five years of age which resulted in a sharp decrease in vaccine coverage nationally (79.8%).⁹⁰

Despite the high coverage and the report of measles elimination, an increase of measles notifications occurred in 2009. 104 cases were notified (rate=0.5 per 100,000

population); 34% were reported to have been acquired overseas. During this year, national MMR1 coverage at 24 months of age was 93.8%, this time with no jurisdiction reaching the 95% target. The national MMR2 coverage increased from the previous year to 83.2% at five years of age.

Measles notifications in 2010 was lower than the previous two years, with 70 cases (0.3 per 100,000 notifications) and 46% of these were reported as being acquired overseas. A multi-jurisdictional outbreak involving nine cases occurred with four transmissions by the index case in an aeroplane. Two subsequent transmissions occurred in healthcare workers.⁹¹ These transmissions occurred in a Queensland hospital.⁹¹ In Queensland, vaccination against measles for healthcare workers is recommended but not mandatory.⁹² Five of the nine cases from this outbreak were hospitalised—three with complications. The severity of measles was also highlighted during this year, with the publication of a report on the death of a previously healthy 22-year old female with no history of having measles infection was diagnosed with SSPE during a post-mortem examination.⁹³

National notified cases are yet to be published in 2011. A number of outbreaks however have been reported. Firstly, a multi-country outbreak occurred when three index cases from New Zealand flew from Singapore to Auckland via Brisbane resulting in eight secondary cases.⁹⁴ Transmission of measles during plane travel to Australia appeared to be an important setting considering four of the most recent outbreak report publications reporting this as the main setting for transmission.^{91, 94, 95} During this year, individuals of Pacific Islander origin were identified as a susceptible population during an outbreak in western Sydney where 46% of the 26 cases were of Pacific Islander origin.⁹⁶

SECTION B

The epidemiology of measles in Australia; 2000–2011

Late draft to be submitted to Communicable Diseases Intelligence

May Chiew, Aditi Dey, Nicolee Martin, Stephanie Davis, Peter McIntyre

SECTION B

The confidentiality of findings in

Alaska, 2002-2011

Abstract

Background:

Since the introduction of measles vaccine to the vaccination schedule, the burden of measles has substantially reduced in Australia. Despite this, a number of recent measles outbreaks have occurred. The aim of this study was to examine the burden of measles in Australia through describing trends of measles infection using the most recent data available on measles notifications, hospitalisations and mortality.

Methods:

Data were obtained from the Australian National Notifiable Disease Surveillance System, the National Hospital Morbidity Database and National Mortality Database to obtain notification, hospitalisation and death data, respectively. Rates per 100,000 population were calculated and compared over time by age group and jurisdiction.

Results:

Since 1993, measles notifications have reduced considerably in Australia. However, between 2000 and 2011, measles notification rates and hospitalisation rates fluctuated. Although children 0–4 years were the most susceptible group in 2000–2002, young adults (20–34 years) and children 10–19 years have appeared to be susceptible. Children 0–4 years and adults 20–34 years were the age groups to have experienced the greatest rates of hospitalisation over the 11-year period. Jurisdictional variation occurred over the study period with differing patterns of notifications and hospitalisations.

Conclusions:

Although a marked reduction in measles notifications and hospitalisations have occurred in Australia since 1993, there is still evidence measles cases are occurring, and a reduction in notification and hospitalisation has not been observed over the past 11 years. Children and young adults continue to be affected by measles infection highlighting gaps that continue to occur nationally. Our results suggest that enhanced immunisation activities are required to vaccinate susceptible individuals and incidence of measles needs to reduce further to be considered eliminated in the country.

Prologue

My role

Upon starting the MAE, one of my first tasks was to conduct an epidemiological review for measles. NCIRS has a contractual arrangement with the DoHA to produce reports on vaccine preventable diseases and the last measles report was published as a Communicable Diseases Intelligence supplement in 2010, as part of the Vaccine Preventable Diseases in Australia report. There was discussion at this stage, however, that the format of the report had should be changed and include some modifications to how hospitalisation data were analysed (i.e. rather than conducting hospitalisation data analysis by financial year and separation date, calendar year and admission date were to be used instead).

I was able to embark on this project immediately as notification and hospitalisation data had already been obtained. Aditi had previously conducted some analysis on the notification data which I have used the results in for Figure 1 and Figure 2. I did however update the number of hospitalisations for Figure 1. I used SAS® to write the programs for notification and hospitalisation data which was my first introduction to analysing notification data using this program.

This project took more time than anticipated, due to a number of other projects that were prioritised due to their public health urgency (measles and *Staphylococcus aureus* outbreaks). However, the delay in completing this project enabled me to update the hospitalisation data to include the whole of 2010.

Lessons learned

This project was a great introduction to measles for me, and auspicious in terms of what would eventuate, in respect to my other measles-related projects. Prior to this project I had little knowledge on the aetiology and pathogenesis of measles and I learnt a great deal about both of these when doing background reading for this analysis. I learnt about the biases of notification data and the importance of standardised case definitions, particularly what role a change in the measles case definition may have played on notification data. Most importantly, I was introduced to the notion of underreporting of cases and the importance of interpreting results of notification data

with the consideration of changes in surveillance activities (such as a change in case definition) and reporting practices.

I learnt the complexities of measles hospitalisation data and that coding of data can at times be inaccurate. I also learnt that the inclusion of all diagnoses for measles in the analysis (i.e. principal and secondary diagnoses for a single admission) can bias the outcome of results.

One important lesson I learnt, and that I previously had no idea of was about the sensitivities around working with small numbers in mortality data. To protect an individuals' confidentiality, small values were randomly assigned by the Australian Bureau of Statistics so that totals in some cases did not equal to the sum of their components. Initially I did not realise that this had been done and found it quite challenging trying to report the number of deaths due to measles as a range.

I also learnt that it would have been useful to have developed a data analysis plan for this project as it would have provided me with clearer directions. I think this was definitely one of my major learning points during the MAE, and one which I think improved as time progressed.

Public health action

This report will be an update of measles epidemiology in Australia and aims to be published in the Communicable Diseases Intelligence journal as a stand-alone paper. It is a follow-up to a previous epidemiological review, however, is important as it provides a national picture of what is happening in Australia with respect to measles incidence and its' burden in the country which has implications towards measles elimination status in the country.

Acknowledgements

I am most thankful to Aditi Dey for providing me with support and guidance throughout this project. I also thank Nicolee Martin from DoHA, for always being available to patiently answer all my questions regarding the notification data and being so generous with her knowledge. I thank Han Wang, the biostatistician at NCIRS for guiding me through all sources of data, increasing my understanding of the caveats of each data source and also assisting in the extraction of the data.

Introduction

Nationally, measles epidemiology has been reported through NNDSS Annual Reports and more recently, Vaccine Preventable Diseases (VPD) Reports which provide an overview of VPDs including measles over a three-year period. Since 2007, an analysis of the epidemiology of measles nationally has not been conducted. Given the 2012 target year for measles elimination in the region, it was timely to provide an updated review of the epidemiology of measles in Australia. The objective of this paper was to determine the burden of measles in Australia through describing trends of measles infection using recent data on measles notifications, hospitalisations and mortality.

Methods

Data Sources

Notifications

Measles is a notifiable condition in all jurisdictions in Australia and both confirmed and probable cases should be notified to health authorities.⁹⁷ A confirmed case of measles requires laboratory definitive evidence or clinical evidence with an established epidemiological link. Alternatively, a probable case of measles require clinical evidence of measles with laboratory evidence suggesting measles infection (specifically measles IgM detection in an unapproved reference laboratory, except if a measles containing vaccine was administered eight days to eight weeks prior to the test).⁹⁸

De-identified national data for both confirmed and probable measles notifications were obtained from the NNDSS from January 1993 to December 2011.⁹⁹ The following fields were included in the analysis: date of diagnosis, age at onset, state or territory of residence and genotype of measles specimen.

Hospitalisations

Data coded for measles using the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification International Classification of Disease (ICD)-10-AM/ICD-10 code B05 were obtained from the Australian Institute of Health and Welfare (AIHW) National Hospital Morbidity Database.¹⁰⁰ The database collects information on patients admitted to public and private hospitals in Australia. Hospital admissions between January 2000 and December 2010 were analysed. Our analysis only includes hospitalisations by admission dates where measles was recorded as principal diagnosis (i.e. the diagnosis primarily responsible for prompting an episode of admitted/residential care or presentation at a healthcare institution) unless otherwise specified. The variables used in the analysis included date of admission, diagnosis, age on admission, state or territory of residence, length of stay and the mode of separation (i.e. the process by which an admitted patient is discharged e.g. discharge, death, transfer or change in care type).

Deaths

De-identified aggregated mortality data (2002-2011) were obtained from the Australian Bureau of Statistics (ABS) National Mortality Database.¹⁰⁰ Registered deaths with measles as the underlying cause based on the cause of death classification ICD-10 were analysed. A more detailed explanation of the methodologies used has been previously described.⁸⁵ To protect an individual's confidentiality, cells in the dataset with small values were randomly assigned meaning a range was provided.¹⁰⁰

Data analysis

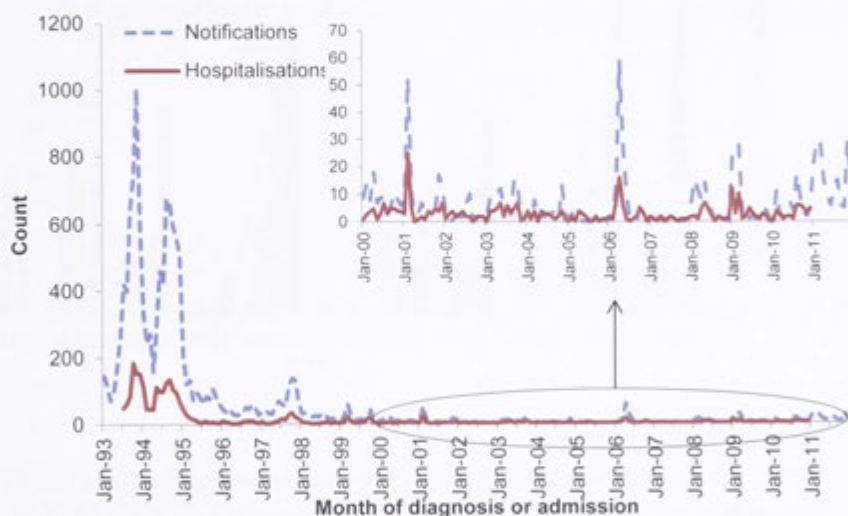
Crude and age-specific annual rates were calculated using mid-year population estimates obtained from the ABS per 100,000 population. Median length of stay was calculated for hospital admissions by days.

Results

Since 1993, measles notifications and hospitalisations have reduced considerably (**Figure B-1**). During 1993 and 1994, notifications peaked with 4678 and 5184 reported cases, respectively. Notifications dropped dramatically over the following years to as low as 10 cases during 2005. Between 2000 and 2011, small peaks were observed in 2001 ($n=132$), 2006 ($n=125$) and, more recently 2011 ($n=190$).

The number of hospitalisations also decreased since 1993, and although peaks in hospitalisations corresponded to peaks in notifications, the number of hospitalisations was much lower than the number of notifications.

Figure B-1. Measles notifications and hospitalisations, Australia, 1993 to 2011, by month of diagnosis or admission*



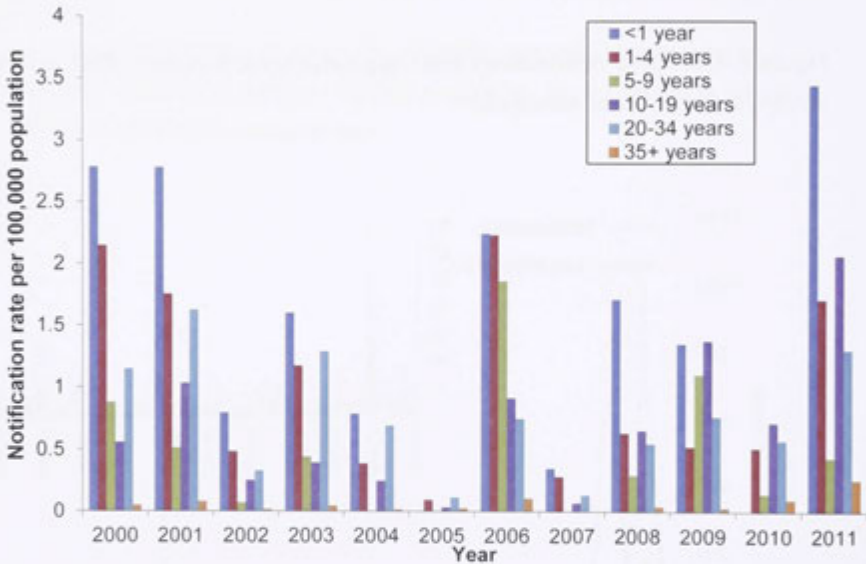
* Hospitalisations (all diagnoses of measles)

Age distribution

When observing measles notification rates by age group in 2000–2011, no specific age group was consistently highest, and rates fluctuated considerably due to the small number of cases (**Figure B-2**). Infants < 12 months of age had the highest notification rates in most years, however, during 2005 and 2010, there were no infant cases notified. In 2011, the notification rate in infants was 3.44 per 100,000 population, the

highest notification rate of all age groups during the twelve-year period. During most years, children 1–4 years of age had the second highest notification rate followed by young adults aged 20–34 years. More recently, children aged 10–19 years of age have had the highest annual notification rates (at 1.38 per 100,000 population in 2009 and 0.72 per 100,000 population in 2010).

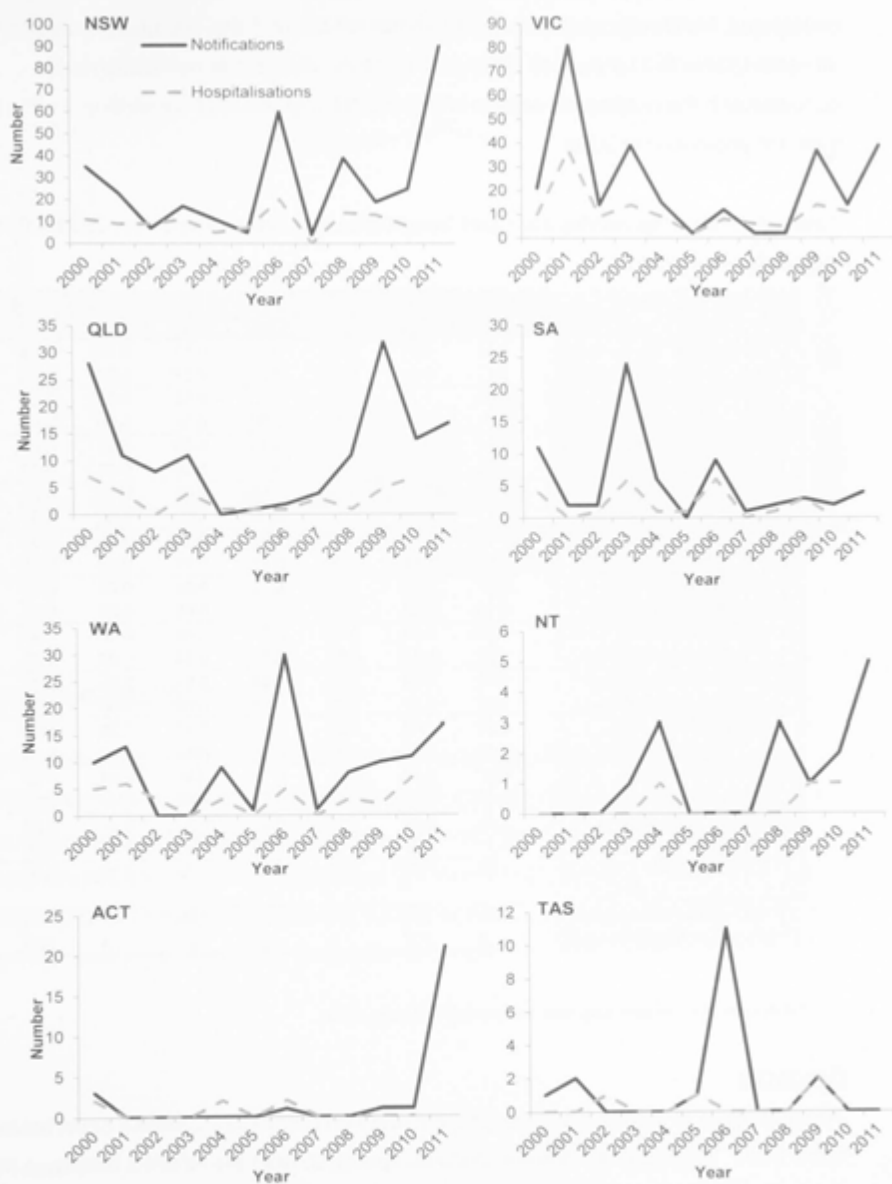
Figure B-2. Measles notification rates, Australia 2000–2011, by age group and year of diagnosis



State and territory variations

Overall, there was considerable variation in notifications among State and Territories. (Figure B-3). Between 2000 and 2011, the three most populous states (New South Wales, Victoria and Queensland) accounted for 76% (752/987) of all measles cases nationwide. New South Wales reported the highest number of measles cases (n=335), of which 27% (n=90) of cases occurred during 2011. During 2009, all States and Territories reported at least one measles case, the only year that this occurred over the twelve-year period. The pattern in hospitalisations for each State and Territory follows a similar pattern to the number of notifications.

Figure B-3. Measles notifications and hospitalisations by jurisdictions**§



* Scales vary between jurisdictions.

§ Hospitalisation (principal diagnosis) data available through 2010

Overall, notification and hospitalisation rates remained low throughout the time period considered. Nationally, notification rates remained below 1 per 100,000 population for all years (**Table B-1**). For each State and Territory, variation in notification rates occurred with the notification rates in NSW, the NT and the ACT exceeding 1 case per 100,000 population in 2011.

Table B-1. Measles notification and hospitalisation rates, Australia, 2000–2011*, by State and Territory

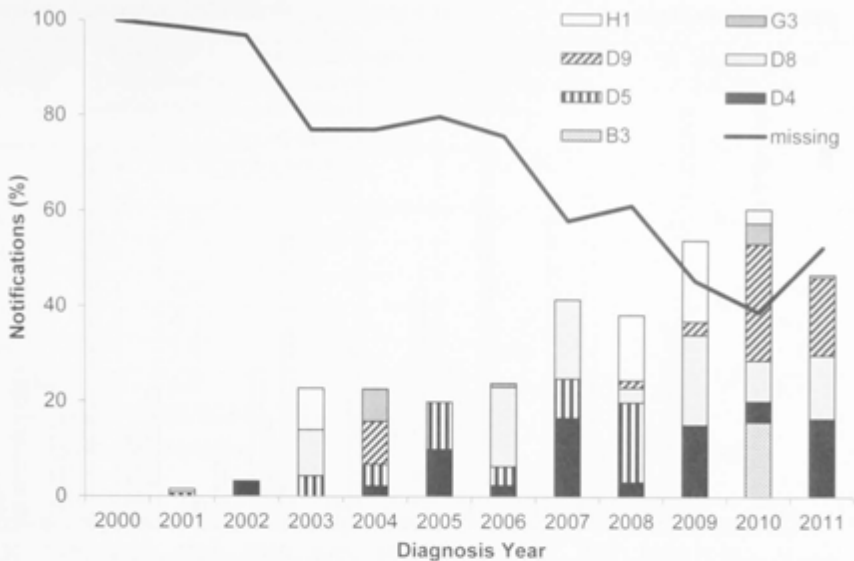
| Year | State or territory | | | | | | | | |
|-------------------------------|--------------------|------|------|------|------|------|------|------|------|
| | NSW | VIC | QLD | SA | WA | NT | ACT | TAS | Aus |
| 2000 Notifications | 0.54 | 0.45 | 0.80 | 0.73 | 0.53 | 0.00 | 0.95 | 0.21 | 0.57 |
| Hospitalisations | 0.17 | 0.21 | 0.20 | 0.27 | 0.27 | 0.00 | 0.63 | 0.00 | 0.20 |
| 2001 Notifications | 0.35 | 1.70 | 0.31 | 0.13 | 0.68 | 0.00 | 0.00 | 0.42 | 0.68 |
| Hospitalisations | 0.14 | 0.78 | 0.11 | 0.00 | 0.31 | 0.00 | 0.00 | 0.00 | 0.29 |
| 2002 Notifications | 0.11 | 0.29 | 0.22 | 0.13 | 0.00 | 0.00 | 0.00 | 0.00 | 0.16 |
| Hospitalisations | 0.14 | 0.19 | 0.00 | 0.07 | 0.16 | 0.00 | 0.00 | 0.21 | 0.12 |
| 2003 Notifications | 0.26 | 0.80 | 0.29 | 1.58 | 0.00 | 0.50 | 0.00 | 0.00 | 0.47 |
| Hospitalisations | 0.17 | 0.29 | 0.11 | 0.39 | 0.00 | 0.00 | 0.00 | 0.00 | 0.18 |
| 2004 Notifications | 0.17 | 0.30 | 0.00 | 0.39 | 0.45 | 1.48 | 0.00 | 0.00 | 0.22 |
| Hospitalisations | 0.14 | 0.18 | 0.03 | 0.07 | 0.15 | 0.49 | 0.61 | 0.00 | 0.11 |
| 2005 Notifications | 0.07 | 0.04 | 0.03 | 0.00 | 0.05 | 0.00 | 0.00 | 0.21 | 0.22 |
| Hospitalisations | 0.10 | 0.04 | 0.03 | 0.06 | 0.00 | 0.00 | 0.00 | 0.21 | 0.06 |
| 2006 Notifications | 0.89 | 0.24 | 0.05 | 0.58 | 1.46 | 0.00 | 0.30 | 2.25 | 0.61 |
| Hospitalisations | 0.30 | 0.16 | 0.02 | 0.39 | 0.24 | 0.00 | 0.60 | 0.00 | 0.21 |
| 2007 Notifications | 0.06 | 0.04 | 0.10 | 0.06 | 0.05 | 0.00 | 0.00 | 0.00 | 0.06 |
| Hospitalisations | 0.00 | 0.12 | 0.07 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.04 |
| 2008 Notifications | 0.56 | 0.04 | 0.26 | 0.13 | 0.37 | 1.36 | 0.00 | 0.00 | 0.31 |
| Hospitalisations | 0.20 | 0.10 | 0.02 | 0.06 | 0.14 | 0.00 | 0.00 | 0.00 | 0.11 |
| 2009 Notifications | 0.27 | 0.69 | 0.74 | 0.19 | 0.45 | 0.44 | 0.28 | 0.40 | 0.48 |
| Hospitalisations | 0.18 | 0.26 | 0.12 | 0.19 | 0.09 | 0.44 | 0.00 | 0.40 | 0.18 |
| 2010 Notifications | 0.35 | 0.26 | 0.32 | 0.12 | 0.48 | 0.87 | 0.28 | 0.00 | 0.31 |
| Hospitalisations | 0.11 | 0.20 | 0.16 | 0.00 | 0.31 | 0.44 | 0.00 | 0.00 | 0.15 |
| 2011 Notifications | 1.25 | 0.70 | 0.38 | 0.24 | 0.72 | 2.16 | 5.71 | 0.00 | 0.86 |
| Total number notifications | 27 | 335 | 15 | 139 | 66 | 17 | 278 | 110 | 987 |
| Total number hospitalisations | 6 | 107 | 3 | 34 | 23 | 4 | 125 | 34 | 336 |

* Hospitalisation (principal diagnosis) data available through 2010

Genotypes

The proportion of measles notifications with data on genotype increased considerably since 2000. (**Figure B-4**). While in 2000 no specimen from the NNDSS database had data on genotype, by 2010, 61% of notifications were genotyped. Of those specimens genotyped, there was no single dominant genotype.

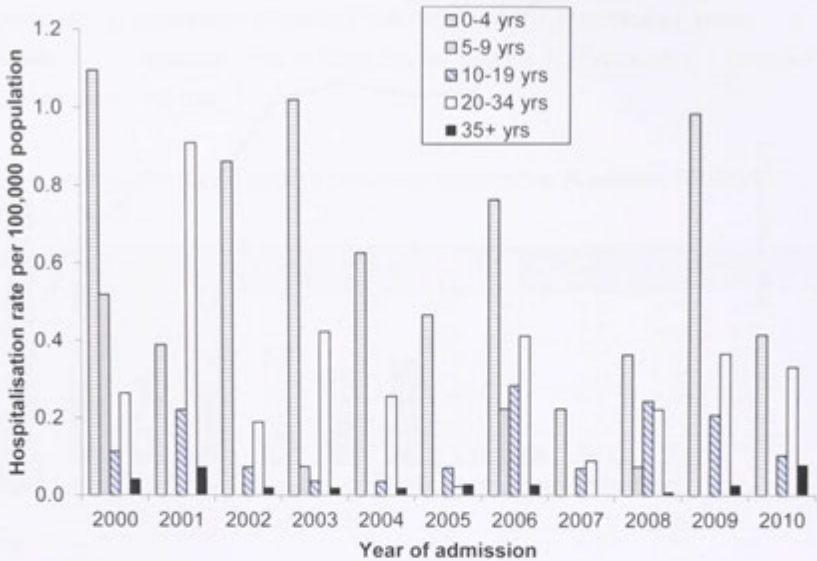
Figure B-4. Proportion of measles notification by genotype, Australia 2000–2011



Severe morbidity and mortality

As observed with notifications, the number of hospitalisations has substantially declined over the past two decades (**Figure B-1**). In terms of age group, the 0–4 year age group had the highest hospitalisation rates for most years (**Figure B-5**). With young adults (aged 20–34 years) having the second highest rate of hospitalisations of all age groups. Hospitalisations in the remaining age groups were low. Overall, adults aged 35+ years had the lowest hospitalisation rates.

Figure B-2. Measles hospitalisation rates, Australia 2000-2010, by age group and year of admission*



* Hospitalisation (principal diagnosis) data available through 2010

Of the 123 measles-related hospital admissions in 2007–2010, 107 (87%) had measles recorded as the principal diagnosis. Complications arising from measles infections were recorded for 17 (16%) admissions (**Table B-2**), of which five were coded as having measles complicated by pneumonia, two cases were coded as measles complicated with intestinal complications and ten as having complications other than pneumonia, otitis media, encephalitis and meningitis. There were no deaths recorded in patients hospitalised with measles between 2007 and 2010.

Table B-2. Selected indicators of severe morbidity for hospitalised cases of measles, Australia, 2007-2010*, by age group

| Age group (Years) | Measles complicated by pneumonia | | Measles with complications other than pneumonia, otitis media, encephalitis or meningitis | | Measles without complications | |
|-------------------|----------------------------------|----------------------|---|----------------------|-------------------------------|----------------------|
| | n | % Total [†] | n | % Total [†] | n | % Total [†] |
| 0-4 | 1 | 3.6 | 2 | 7.1 | 25 | 89.3 |
| 5-9 | 0 | - | 0 | - | 1 | 100.0 |
| 10-19 | 1 | 5.6 | 1 | 5.6 | 16 | 88.9 |
| 20-34 | 2 | 4.3 | 2 | 10.5 | 40 | 85.1 |
| 35+ | 1 | 7.7 | 4 | 30.8 | 8 | 61.5 |
| All ages | 5 | 4.7 | 12 | 11.2 | 90 | 84.1 |

* Hospitalisation (principal diagnosis) data available through 2010

[†] % of total in the age group

Length of stay per admission by age group is displayed in Table B-3. Between 2007 and 2010, hospital separations accounted for 306 bed days. The median length of stay was three days with adults aged 35+ years age group having the longest median length of stay in hospital (four days).

Table B-3. Length of stay per admission of measles hospitalisation by age group, 2007-2010[§]

| Age group (year) | Hospital admissions | | Median length of stay (days) | |
|------------------|---------------------|-------------------------------|------------------------------|-------|
| | n | rate per 100,000 [‡] | n | range |
| 0-4 | 28 | 0.50 | 1.5 | 1-6 |
| 5-9 | 1 | 0.02 | 1 | 1-1 |
| 10-19 | 18 | 0.16 | 2 | 1-6 |
| 20-34 | 47 | 0.25 | 3 | 1-8 |
| 35+ | 13 | 0.03 | 4 | 1-8 |
| Total | 107 | 0.12 | 3 | 1-8 |

[§] Principal diagnosis (hospitalisations)

[‡] Average annual age-specific rate per 100,000 population

Between 2002 and 2011, there were one to four deaths reported in the National Mortality Database with measles as the underlying cause of death. These deaths were registered in 2010 and occurred in males only.

Discussion

Our results provide an overview of the burden of measles in Australia over the last twelve years. Overall, the notification rate fluctuated reducing to less than one case per million population twice during the study period, a previous indicator of low incidence set by the WHO required to reach elimination.⁸⁹ More recently however, this indicator was updated to not include a threshold. The revised indicator states countries where measles should have very low incidence of confirmed cases – which our results indicate have occurred.

From our results, it was evident that the 0–4 year age group is a vulnerable population for measles infection and hospitalisations. It has been well-documented that measles is predominantly a childhood disease. However, from our data, infants younger than 12 months of age, in most years have been the age group most affected by measles, highlighting their susceptibility. One explanation for this could be the decline in maternal antibodies in infants, with a minimum level at 7–9 months of age observed.¹⁰¹ Moreover, the concentration of antibodies against measles in pregnant women derived from vaccine has been found to be significantly lower than antibodies derived from natural infection.²⁶ In addition, a modelling study has predicted that by six months of age, 95% of infants with naturally derived maternal antibodies would be susceptible to measles due to the waning of maternal antibodies. It has been postulated that because measles is becoming rare, the lack of natural boosting through exposure of wild virus in both vaccinated women and women with past infection has consequently resulted in infants becoming more susceptible. It is thus important that timely vaccine uptake among infants occurs at the recommended 12 months of age. During outbreaks, the first dose of measles can be administered early, with two subsequent doses required after 12 months of age due to concerns of interference with maternal antibodies.

In the above discussion, the susceptibility of infants was outlined but it is also important to consider the susceptibility in children aged 1–4 years. Previously under the NIP, the booster dose of MMR was administered at 4 years of age. In 2008, it was recommended that the booster should be brought forward to 18 months given the number of notifications in the 1–4 year age group and the potential to improve vaccine uptake.²³ This recommendation was not implemented under the NIP until July 2013 and aims to protect children against measles at an earlier age.²²

Interestingly, between 2009 and 2010, individuals aged 10–19 years had the highest notification rates which increased in 2011. This age group would have been born between 1990 and 2001 and should have been captured during the MCC. However, it might be that a proportion of individuals in this age group (those born between 1990–1992) were too young to be eligible for MMR2 given at 10–14 years between 1995 and 1998 and too old for MMR2 when the dose was brought forward to four to five years of age in 1998, and thus missed out on the booster dose of vaccine. This was highlighted during a recent high-school based outbreak (ten cases in a single high-school).⁹⁶ Additionally, detailed demographic information on the 10–19 year age group would assist in considering risk factors that may be associated with infection such as ethnicity (eight of the ten cases were of Pacific Islander origin⁹⁶). This would allow for more targeted interventions to be piloted promoting vaccination uptake in this age group.

Our study supports previous literature which identified young adults as susceptible cohort. Those born between 1968 and 1982 (21–45 years) are particularly susceptible as low vaccine coverage existed when they were infants and natural immunity against infection was waning.⁷² Furthermore many in this cohort were ineligible for the booster dose as they exceeded the 10–16 year eligibility age when it was offered between 1994 and 1998. Young adults are often mobile and well-travelled with a number of past outbreaks occurred following the importation of measles by a young adult traveller from measles endemic countries.^{61, 75, 79} Although a targeted young adult measles campaign was conducted in 1999, it was deemed to be unsuccessful in changing immunity, possibly due to the lack of funding for advertising and planning.⁷³

As most outbreaks in Australia begin with an importation of measles from an endemic country, it is essential that measles immunity status be assessed when patients attend clinics to receive vaccinations for international travel. Currently, all individuals born during or after 1966 who have not acquired natural immunity or received two doses of MMR are recommended to be vaccinated before travelling.²² Of further concern is whether travellers present to a healthcare facility for pre-travel advice. In a study of 17 353 ill returned travellers who presented to one of the 30 participating travel or tropical medicine clinic around the globe, 50% had documented pre-travel health advice.¹⁰² Given the low proportion of travellers seeking pre-travel health advice, it is necessary to think of other mechanisms to raise the awareness of the risk of measles in unvaccinated individuals travelling to measles endemic countries. Health advice upon

booking a flight or travel insurance may be possibilities; however, further research is necessary.

Moreover, an Australian-based study found that 4% of recently returned travellers who presented to two hospitals were vaccinated against MMR over a six-year period (1998–2004) in a group of 917 travellers.¹⁰³ Although MMR is currently recommended in travellers born after 1966 who have not had two doses of measles containing vaccine,²² the proportion travellers in this category who receive MMR is unknown. Moreover it is unclear whether immunisation providers recommend vaccination. It would be of value to conduct a qualitative survey on the attitudes and behaviour of general practitioners towards pre-travel advice, particularly for measles.

Clearly, a number of susceptible populations exist in Australia and consequently this may lead to outbreaks in these populations. To determine whether cases are linked, it is important that genotyping of specimens occurs. Additionally, genotyping of specimens indicates the origins of the genotype and examines whether there are particular strains circulating in a country— especially important in the verification of measles elimination.⁵¹ Our results on completeness of the data field 'genotype' indicate that during the earlier years, genotyping was not conducted. A previous study, however, suggest that genotyping did indeed occur and during 2000 and 2001. Between 2000 and 2001, D7, G2, H1 and D5 were observed to be circulating in Australia⁸² but for some reason, were not captured in the NNDSS dataset. A review of the NNDSS measles dataset to assess the quality of this data field is recommended. This is because the completeness is of particular importance in demonstrating whether a circulating measles strain exists.

A number of limitations in the analysis warrant caution in interpreting the results. Firstly, in general notification data is considered not representative of all cases in the community due to not all cases presenting for health care and/or having the correct diagnostic test taken. However, this is unlikely to occur for measles as it is assumed most cases would attend a healthcare facility due to the signs and symptoms of the disease.

Secondly, a unique identifying code which links NNDSS and AIHW morbidity data does not exist.

In general, coding errors may occur in hospitalisation data, particularly when coding conditions that an individual is hospitalised for. A Victorian based study found that the discrepancy rate in coding field amongst hospital morbidity data increased the rarer the condition.¹⁰⁴ Our data also highlighted these discrepancies as in some instances, the number of hospitalisations exceeded number of notifications suggesting either the under-reporting of measles notifications and/or the miscoding of hospitalisations as measles.

Lastly, the case definition for measles was amended in 2004. Prior to 2004, a confirmed case of measles could include a clinical diagnosis of an illness characterised by measles. As many conditions may present with similar symptoms to measles, the specificity of this case definition is likely to have been low and subsequently led to an overestimation of true measles cases.¹⁶

Although the last reported death due to measles occurred in 1995, between 2002 and 2011 period, one to four deaths were recorded in 2010. Unfortunately, we have no further information on which complications occurred, and whether there were specific factors that made these cases more susceptible such as pre-existing co-morbidities and/or extremes of age. A recent publication⁹³ indicated that during the study period, a 22-year old died from SSPE in Western Australian hospital, however, this was not captured in the AIHW morbidity and National Mortality dataset based on sex and age. It is not known how sensitive the dataset is in capturing deaths where the main cause is measles

Conclusions

The rates of notification and hospitalisation of measles in Australia have fluctuated over the last 12 years, with gaps in immunity continuing to occur in children 1–4 years and more recently, those aged 10–19 years. This suggests that enhanced immunisation activities would be beneficial for certain groups. . Measles notification rates have remained above previous WHO criteria of below one per million population in ten of the 12 years of the study period..

SECTION C

Evaluation of the measles reproduction number (R) as a practical means to track maintenance of measles elimination using routine notification data – the Australian experience

Late draft of peer review paper accepted for publication in the Bulletin of the World Health Organization

May Chiew, Heather F Gidding, Aditi Dey, James Wood, Nicolee Martin, Stephanie Davis, Peter McIntyre

***“The Western Pacific is on the verge of becoming the second
WHO region, after the Americas, to be certified measles-free”***

– Dr Margaret Chan

Keynote address to the Regional Committee for the Western Pacific,
Sixty-third session
Hanoi, Viet Nam
24 September 2012

Abstract

Background:

Global targets for measles elimination have now been established by all World Health Organization (WHO) regions. Demonstrating that R , the average number of secondary cases from an infectious case remains below one is a widely accepted means to track maintenance of measles elimination. We evaluated three methods to calculate R using routinely collected notification data.

Methods:

Using data from Australia's National Notifiable Disease Surveillance System, R was estimated for the years 2009–2011. Three methods were used to estimate R : 1) Proportion of imported cases; 2) Distribution of outbreak sizes; and 3) Distribution of generations of spread. Proportions of completeness of the required notification data fields were also examined.

Results:

Between 2009 and 2011, there were 367 notified cases in Australia, a mean annual rate of 5.5 per million population. Data completeness was 100% for importation status but 77% for outbreak reference number. We estimated R to be below one for all years and methods used. Based on the proportion of imported cases, $R = 0.65$ (95% CI=0.60–0.70), based on distribution of outbreak size $R=0.64$ (95% CI=0.56–0.72), and based on generation of spread $R=0.47$ (95% CI=0.38–0.57).

Conclusions:

We obtained consistent estimates of R by all three methods, enhancing confidence in their validity. Importation status is the most straightforward surveillance data element to collect and should be applicable to a wide range of countries as a practical means to monitor elimination status.

Prologue

My role

Heather Gidding, a past MAE scholar and former epidemiologist at NCIRS, in April 2012, returned to work one day a week at NCIRS on a number of projects. Due to my work on an epi-review of measles in Australia at that time, she approached me to work on a project using measles notification data to estimate the reproduction number (R) for measles. Heather has conducted numerous studies using serosurveillance data to estimate R , as a co-author on a landmark study in Australia providing evidence of measles elimination and has authored numerous studies on measles control.

This project would involve the use of sub-branching critical models to estimate R which was unfamiliar territory to me and a difficult concept to grasp. It was however a collaborative project, including Heather, Aditi, Dr James Wood a modeller from University of New South Wales and Ms Nicolee Martin from the Department of Health and Ageing (DoHA).

I was involved in conducting the literature review for this project, developing the first draft of the project proposal, cleaning the data, conducting descriptive analysis, developing the algorithm to identify potentially missed outbreaks, using the algorithm in preparation for the modelling analyses and drafting the manuscript.

It must be made clear that the estimates of R were a collaborative effort and close guidance was provided by Heather and James during the analysis. I conducted the analyses to estimate R for the methods proportion of imported cases and distribution of outbreak sizes whilst James conducted modelling analysis to estimate R by distribution of generations of spread. I had no involvement in the analysis that James conducted.

Lessons learned

One of the primary lessons that I learnt due to this project was the potential use of national notification data beyond the scope of what I had previously known, when a high quality surveillance system exists.

I also feel I have grasped some sense of modelling, due to this study, including the complexities of modelling and that is about estimations rather than 'the truth'.

This project enabled me to witness and belong to an extremely supportive and encouraging environment. I have learnt, in many respects, how I hope to be further down in my career if ever I were to mentor students. Communication between main co-authors was an important reason this project progressed incredibly smoothly and it has made me realise how important communication is in the success of your work.

Additionally, the process of preparing a manuscript for this project allowed me to understand that the choice of journal for submission is extremely important in how the paper is framed and ultimately, the main messages of the paper.

Public health action

The results of this project will form part of the lines of evidence that is being compiled by the measles elimination working group for the verification of measles elimination in Australia. The potential impact of measles elimination in Australia, if formally verified, will contribute to the World Health Organisation (WHO) Western Pacific Regional Office (WPRO) in their target for measles elimination in the region in 2012. Furthermore, the priority of measles elimination in all WHO regions is high, with worldwide measles eradication considered feasible in the not too distant future.

Acknowledgements

First and foremost, I am extremely grateful to Heather and James Wood for their guidance and patience during the most critical part of this project, the analysis. Without them, this project could not have been completed. I also would like to thank Aditi for always encouraging me to push harder and aim higher. Without this drive, I would not have been successful in presenting this project at the TEPHINET Global Conference—one of the highlights of my very short epidemiological career, thus far. I am also most thankful to Nicolee for being instrumental in the high quality of the data and happy to answer any questions I had for her. And also to Andrew Hayen from the University of

New South Wales, who generously provided feedback on the methodology of this project. Lastly, the collaborators in this project were an utmost joy to work with and provided me with such valuable feedback and encouragement during all stages of the project.

Introduction

Between 2000 and 2010, the global burden of measles reduced considerably, with annual measles incidence and mortality decreasing by 66% and 74%, respectively.³ The implementation of childhood and supplementary immunization activities by World Health Organization (WHO) Member States has largely contributed to these declines. As a result, all WHO Regions have set target dates for measles elimination¹⁰⁵, most recent being the South-East Asian Region.⁵ At present, the Region of the Americas is the only WHO Region to have achieved elimination, reporting the interruption of endemic measles transmission in 2002.¹⁰⁵

Three years after the declaration in the Americas, the WHO Regional Office for the Western Pacific (WPRO) adopted a resolution, setting 2012 as the target year for measles elimination in the region.⁴⁷ Several countries have made significant progress towards this goal, including Australia.¹⁰⁶ Over the past two decades, the national incidence of measles has declined dramatically, following a number of national measles strategies, including the 1998 Measles Control Campaign and lowering the second dose of measles containing vaccine to four years of age.^{79, 107, 108} This led to a report that indigenous measles transmission had been eliminated in Australia⁶ with the authors' reasoning that Australia had satisfied most of the WPRO criteria to justify the elimination of measles.⁶

One approach to monitoring measles elimination is by estimating the reproduction number (R). R is the average number of secondary cases that results from an infectious case in a particular population (Box 1).¹⁰⁹ When R is below one, the number of cases reduces with every generation and, if maintained, elimination is considered to have occurred.¹⁰⁹

There are a number of methods to estimate R , including the use of serosurveillance data, the early epidemic phase growth rate and notification data.^{63, 109, 110} In Australia, three national serosurveys have been conducted previously.^{111, 112} Serosurveys however, can be time consuming and costly¹¹³ and in developing countries, may not be feasible. Alternatively, routinely collected notification data can be used to estimate R on a regular basis with minimal resources required. These methods were described by De Serres et al.¹⁰⁹ and uses the following data to estimate R : 1) the proportion of cases imported; 2) the distribution of outbreak sizes and; 3) the distribution of the number of

generations of spread in each outbreak.¹⁰⁹ An assumption required when using these methods is that elimination has already been achieved.

Methods based on routinely collected notification data have been used to differing extents internationally^{114, 115} and in Australia. The United States (US) and Canada both reported the interruption of indigenous measles transmission by 1998 and used the methodology described by De Serres et al. to assess elimination.^{114, 115} England and Wales also claimed elimination and used the distribution of outbreak sizes (1995–2001) to estimate R .¹¹⁶ In the Australian state of Victoria, notification data (1998–2003) were used to estimate R using the distribution of outbreak size and generation of spread ($R=0.87$ and $R=0.73$, respectively).¹¹⁷ More recently, National Notifiable Diseases Surveillance System (NNDSS) data (2001–2006) in Australia were used to estimate R using the proportion of imported cases ($R=0.90$); the authors concluded, however, that the incompleteness of data may have resulted in the overestimation of R .⁶ There have been considerable improvements in completeness of notification data since 2009. Therefore, the aim of our study was to apply three methods for estimating R using routinely collected notification data and highlight the utility of these methods in lower resource countries as a practical means to monitor elimination status.

Methods

Notification data

In Australia, measles is a notifiable disease in all States and Territories. Under public health legislation, clinicians and laboratories are required to notify their respective health authorities of a suspected, probable or confirmed case of measles.⁹⁷ Additional information on confirmed measles cases are collected by health authorities during follow-up investigations and forwarded to the NNDSS. Confirmed cases of measles require either laboratory definitive evidence of measles infection or both clinical and epidemiological evidence.⁹⁷

De-identified data were obtained from the NNDSS dataset for all notified measles cases between 2009 and 2011. Data fields used in the analysis included 'place (country) of acquisition', 'outbreak reference number' (Box 1), date of symptom onset (if missing, diagnosis date was used).

Box 1. Definitions

1. Importation¹¹⁸: a case public health authorities believe was acquired overseas based on international travel in the period prior to rash onset.

2. Generation of spread of an outbreak¹¹⁴:

- **Same generation** : disease onset date between the first and last case was 0–6 days apart
- **One generation of spread**: disease onset date between the first and last case was 7–14 days apart
- **Two generations of spread**: disease onset date between the first and last case was 15–24 days apart
- **Additional generation of spread**: 10 days difference between the disease onset date of the first and last case added an extra generation

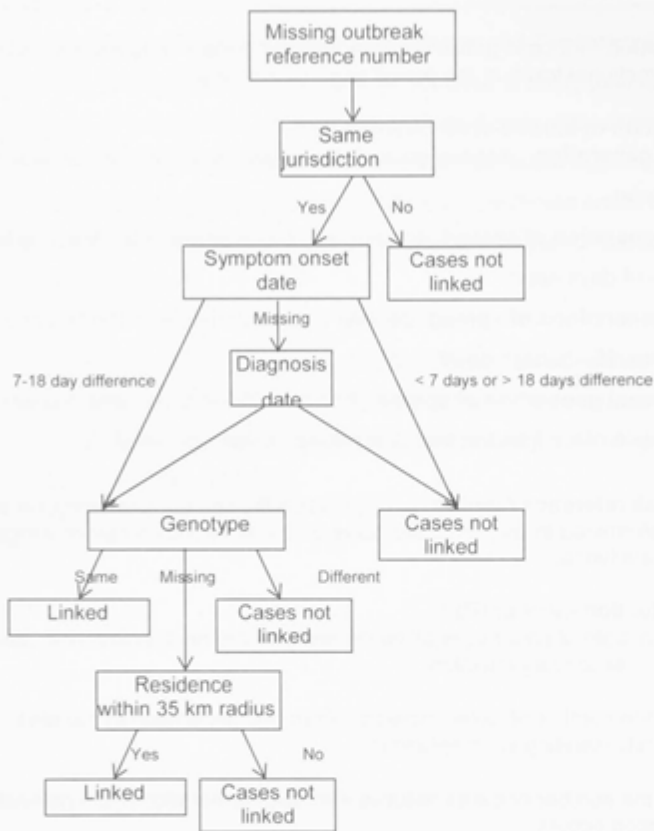
3. Outbreak reference number: a unique identification number assigned to cases which were determined to be part of the same outbreak based on epidemiological (and/or virological) evidence.

4. Reproduction number (R)¹⁰⁹:

- **R= 1**: a state of endemic equilibrium exists where on average, one case results in one secondary infection
- **R > 1**: the number of cases increases from one generation to the next, potentially resulting in an epidemic
- **R < 1**: the number of cases reduces with each generation and if maintained elimination occurs

An algorithm was developed to link cases together where data field 'outbreak reference number' was missing '(Figure C-1).

Figure C-1. Algorithm link cases together where data 'outbreak reference numbers' was missing to identify possible measles outbreaks



If 'place (country) of acquisition' was overseas, cases were considered sporadic unless they had the earliest onset date of an identified outbreak and all other cases were locally acquired. If more than one case was acquired overseas in the same outbreak, the imported case most temporally similar to locally acquired cases was considered the index case whilst the other imported case was considered sporadic. All remaining cases where 'place of acquisition' was local and 'outbreak reference number' was missing were defined as sporadic. For cases belonging to the same outbreak, the generation of spread of infection was derived from a previous algorithm (**Box 1**).¹¹⁴

Estimating R

Three methods were used to estimate R for the combined years 2009 to 2011 and for each individual year (2009; 2010; 2011). In method one, R was estimated as $1 - p$, where p = proportion of cases imported (using the data field 'place of acquisition'). This method is based on the observation that if each initial case infects R persons, the second generation will contain R^2 persons and so on, with the total number of cases forming a geometric sum with value $1/(1-R)$. And hence, with some simple algebra¹⁰⁹ R can be estimated

For the second and third methods, R was estimated through fitting a subcritical branching process that models the spread of infection with reproduction number R to the observed distributions of outbreak sizes and generations of spread, respectively.¹¹⁹ For details of the branching process model, please refer to the paper by De Serres.¹⁰⁹ Maximum likelihood estimation was used to obtain estimates for R. Stata version 12 ®¹²⁰ was used to estimate R for the distribution of outbreak sizes, while estimates of R using the distribution of the generations of spread were calculated in Matlab version R2012 ®.¹²¹

For all three methods, 95% confidence intervals were estimated using a normal approximation based on the estimated standard errors.

All of these approaches are based on the assumption that $R < 1$ and are only appropriate in settings where measles incidence is low. In addition, for the second and third methods, it is assumed that the reproduction number for each individual is Poisson distributed with mean R and thus (non-random) heterogeneity between individuals is ignored.

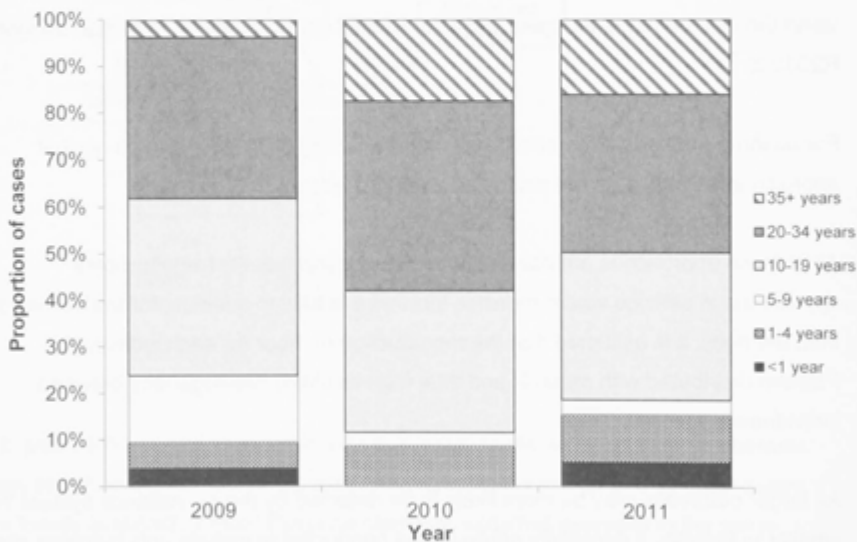
As larger outbreaks may be more likely to be detected by the surveillance system than smaller outbreaks, a sensitivity analysis was conducted to include only outbreak sizes of ≥ 3 cases.

Results

Notification data

Between 2009 and 2011, there were 367 notifications of measles in Australia (mean notification rate 5.5 per million population) with 105 cases in 2009 (notification rate 4.8 per million population), 69 cases in 2010 (notification rate=3.1 per million population) and 193 cases in 2011 (notification rate=8.5 per million population). Most cases occurred in individuals aged 10–19 years and 20–34 years (**Figure C-2**). Thirty-five per cent (n=128) of cases were acquired overseas and 41% (n=150) were epidemiologically linked to an imported case. The data fields 'place of acquisition' and 'outbreak reference number' were 100% (n=367) and 77% (n=283) complete, respectively. Fifteen sporadic cases had a complete 'outbreak reference number'.

Figure C-2. Distribution of confirmed measles cases by age group in Australia, 2009–2011



Source: National Notifiable Diseases Surveillance System, Australia

Of the 84 cases with missing 'outbreak reference number', 19 (23%) were reclassified as belonging either to an identified outbreak or were linked together as part of an outbreak previously not identified. Seven cases were linked based on jurisdiction, time and identical genotype compared to 12 cases that were linked by jurisdiction, time and

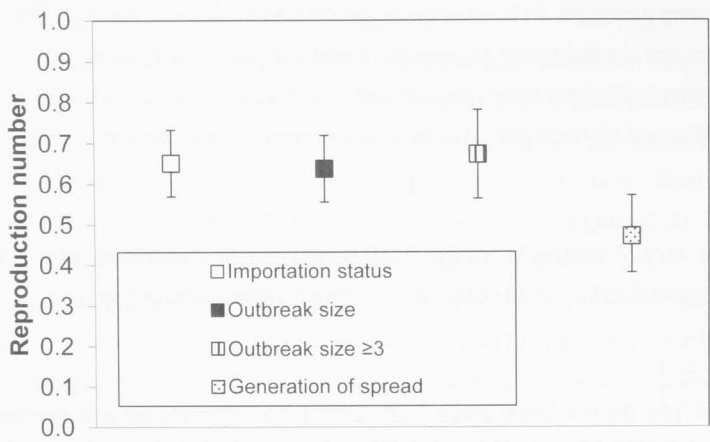
proximity of residence. The remaining 65 cases with missing 'outbreak reference number' were considered to be sporadic. Of these, 83% were acquired overseas and 25% had missing genotype, 21% were genotype D8 and 16% were genotype D9. The algorithm was also applied to the 15 sporadic cases with a complete 'outbreak reference number' with 2 sporadic cases linked to a cluster of two cases based on jurisdiction, time and identical genotype and subsequently considered an outbreak of four cases

Overall, there were 55 outbreaks (range: 2–25 cases) and 78 sporadic cases in 2009–2011. The longest duration of an outbreak was seven generations (67 days).

Estimation of R

The values of R for the combined years 2009–2011 for all methods were significantly below 1. Little difference was observed between using the methods proportion of importations and outbreak size to estimate R (**Figure C-3**). Further, R estimates, when restricting outbreak size to three or more cases and when no restrictions were applied appeared similar ($R=0.67$ 95% CI= 0.56–0.78 and $R=0.64$ 95% CI=0.56–0.72, respectively). However, the generations of spread method provided a lower R estimate (0.47 95% CI= 0.38–0.57) than the other methods used.

Figure C-3. Estimates of the reproduction number including 95% confidence intervals in Australia, 2009-2011



Source: National Notifiable Diseases Surveillance System, Australia

Similarly, for individual years all estimates of R were below 1 and there was little difference in estimates across time and method (Table C-1). Again, the method of generations of spread provided the lowest annual estimates. The lowest value of R was observed in 2009 for the distribution of generations of spread (0.38 95% CI: 0.19–0.56). The highest value of R was observed from the sensitivity analysis conducted on outbreak size in 2009 (0.78 95% CI: 0.57–1.00). This estimate was the only result where the upper confidence interval reached 1.00. Similar R estimates were obtained when including and excluding outbreaks with three or more cases.

Table C-1. Estimation of R in Australia by individual year, 2009-2011, NNDSS data

| Methods | 2009 | | 2010 | | 2011 | |
|---|------|-----------|------|-----------|------|-----------|
| | R | 95% CI | R | 95% CI | R | 95% CI |
| Proportion of imported cases | 0.66 | 0.57-0.75 | 0.55 | 0.43-0.67 | 0.68 | 0.62-0.75 |
| Distribution of outbreak sizes | 0.65 | 0.49-0.80 | 0.59 | 0.41-0.78 | 0.65 | 0.53-0.76 |
| Distribution of outbreak sizes ≥ 3 cases | 0.78 | 0.57-1.00 | 0.65 | 0.40-0.90 | 0.62 | 0.47-0.76 |
| Distribution of generations of spread | 0.38 | 0.19-0.56 | 0.50 | 0.29-0.70 | 0.50 | 0.38-0.63 |

Discussion

During 2009 to 2011, R estimates using national notification data remained below one, providing good evidence that measles elimination is being maintained in Australia. These findings are consistent with estimates obtained using the 2002 serosurvey data, which estimated R to be 0.69 and the prediction that between 2003 and 2012, R would remain below 0.80.¹²² Our conclusion that measles elimination is being maintained is further supported by high measles vaccine coverage rates and the absence of an endemic circulating genotype for many years in Australia.^{82, 123}

Similarities in R estimates between the three methods used in this study and that of the serosurvey suggest that estimates of R using Australia's surveillance data are valid. Additionally, there was little difference between the estimates of R when restricting outbreak size ≥ 3 cases and when no restrictions were applied, which indicates a high level of sensitivity of the surveillance system in detecting both small and large outbreaks.

There was however, some variation for the estimates of R between the three methods used. The highest value of R was observed in 2009 for the distribution of outbreak size ≥ 3 cases per outbreak and this was the only value where the upper confidence interval reached 1.00. A large proportion of cases in 2009 were sporadic or clusters of two resulting in only seven outbreaks left in the analysis, the largest outbreak throughout the time period ($n=25$) also occurred during this year. Consequently, this method resulted in wide confidence intervals and a high R estimate.

It was expected that the R estimates would be highest using the proportion of imported cases method due to an underestimation of the number of cases arising from contact with international visitors, as was observed in similar studies conducted in the US and Canada.^{109, 114, 115} The estimate of R based on importation status in the US was 0.68 (95%CI=0.30–0.78) compared to 0.51 (95%CI=0.44–0.59) using the distribution of outbreak size.¹¹⁴ Similarly, the estimate of R based on importation status in Canada was 0.87 (95%CI= 0.76–0.98) compared to 0.82 (95%CI=0.72–0.93) using the distribution of outbreak size.¹¹⁵ Our estimates, however, were comparable to the estimates obtained from the other two methods. The 100% ascertainment of 'place of acquisition' is possibly the reason for our comparable results. In contrast, the completeness of reporting imported cases (1997–2001) in the US was only 40%.¹²⁴ It

is likely that estimates of R using the proportion of imported cases method provided an accurate R estimate for Australia due to a sensitive surveillance system and complete data on place of acquisition.

An important difference to consider when comparing our estimates with those from the US and Canada relates to the definition of an imported case. An importation in the US required travel outside the US 18 days prior to rash onset (unless date of symptom onset was ≥ 7 days following the symptom onset date of a travelling companion).¹¹⁴ An importation in Canada required exposure outside Canada 7–21 days prior to rash onset not linked to a local transmission.¹²² Australia's definition of an importation (Box 1) involves assessment on a case-by-case basis using epidemiological and virological evidence and may have been more sensitive and less specific than either of these definitions. For example, a case with prior travel to the Philippines, 23 days before symptom onset in Australia was considered imported.¹³ In the US and Canada, however, this case would not be considered imported.^{114, 115} Nevertheless, overestimations are unlikely as health authorities usually conduct extensive investigations for each case.¹³ The use of a consistent definition for importation status among health authorities both in Australia and internationally would provide more comparable R estimates. As recording of importation status requires minimal additional resources and any underestimation of the proportion imported would only overestimate R, we recommend low- to middle-income countries initially focus on collecting this variable to monitor their elimination status.

R estimates obtained from the distribution of generations of spread were consistently found to provide lower estimates in Australia and the US ($R=0.44$ 95%CI=0.36–0.52) compared to the other methods used. One explanation for the lower estimates is that the generations of transmission for both countries were derived from an algorithm, possibly making R estimates using this method less valid.¹¹⁴ For example, in 2009–2011, the longest duration of an outbreak (67 days) in Australia was calculated to be seven generations. However, based on an incubation period of 18 days, the generations of transmission of this outbreak could have been as low as four generations. Recording the number of generations of transmission would improve the validity of estimates of R using this method.

In our study, R estimates for the distribution of outbreak size and distribution of the generations of spread may also have been an overestimate of the true value. Nineteen cases with a missing 'outbreak reference number' were assigned to a particular outbreak based on an algorithm (**Figure 1**). We also used the algorithm on sporadic cases with a complete 'outbreak reference number' to assess whether they may have been part of an outbreak. This was conducted as some health authorities automatically assign an 'outbreak reference number' to all cases of measles regardless of whether the case was known to belong to an outbreak or not. These cases may have wrongly been assigned to an outbreak potentially overestimating R . However, as measles is such a rare disease in Australia, it is likely that cases with temporal and geographical similarities are indeed linked. Moreover, the high sensitivity of the surveillance system made the detection of most measles cases likely. Hence, it is unlikely that a large number of cases were missed, which would have resulted in an underestimation of R .

Completeness of surveillance data is imperative to obtain accurate estimates of R . In comparing our results with Canada and the US, it is important to note that our data were more recent (2009–2011) than those used in Canada (1998–2001)¹¹⁵ and the US (1997–1999)¹¹⁴. It is likely that the completeness of data for both countries have improved since these studies were conducted. However, to date these studies are the most recent to be published. In Australia, over the three-year period analysed, completeness of the data field 'place of acquisition' was 100%. The data field 'outbreak reference number', however, was incomplete. This in part is because most jurisdictional health authorities do not assign unique outbreak reference numbers to known sporadic cases (personal communication, Nicolee Martin). If all known sporadic cases were assigned reference numbers they could be more accurately differentiated from cases where a link to an identified outbreak was undetermined providing a more accurate R estimate. However, recording 'outbreak reference number' and the number of generations of spread requires more extensive case follow-up to enable linkage between cases, and may be more challenging to collect in low- and middle-income countries.

The models used in our study have a number of potential limitations. We assumed homogeneity in susceptibility and the mixing of populations.¹⁰⁹ Past outbreaks have identified susceptible sub-populations in Australia, including young adults and infants too young to be immunised.^{72, 73, 125} Therefore, R may exceed one in certain sub-

populations. However, our results are similar to R estimates using serosurveillance data,¹²² which take into account population dynamics. Despite these limitations, these methods provide a suitable means to monitor the status of elimination in Australia as a whole, on a regular basis through the use of high quality national notification data and could potentially be applied in lower-resource settings too.

Notification data have the potential to play an important role in verifying measles elimination, especially when all WHO Regions are working towards elimination by 2020.^{4, 5} As high quality surveillance is an essential criterion for verification,⁵¹ it should be feasible for all countries aiming for verification to produce valid R estimates using the methods described in this paper, particularly through collecting importation status; as ongoing evidence for the maintenance of a country's elimination status.

Conclusions

Our results provide evidence of sustained measles elimination in Australia and suggest the validity of using notification data to monitor measles elimination where a sensitive surveillance system exists. Collecting the importation status of all cases during case investigations in low- and middle-income countries is simple and the methodology to estimate R straightforward. As global measles activities shift focus from measles control to measles elimination, the use of notification data, particularly importation status to estimate R has the potential to be an important component of the verification process by WHO Regional Offices, particularly in low-resource countries.

Acknowledgements:

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Background

As a result of the COVID-19 pandemic, many

businesses have been forced to close.

Some businesses have been able to

continue to operate, but at a loss.

Others have been able to continue to

operate, but at a loss.

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Conclusion

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SECTION D

*Measuring discard rates for measles in
New South Wales; an indicator of
quality surveillance*

Abstract

Background:

A measurement of the quality of measles surveillance includes examining the rate of suspected measles cases that end up as negative results (laboratory discard rate). Ensuring adequate investigation of suspected measles (≥ 2 non-measles cases per 100,000 population) is imperative to high quality surveillance which forms part of the criteria necessary to verify measles elimination. The objective of this study was to measure the discard rate in NSW to determine whether NSW is satisfying one of the criteria necessary for measles elimination.

Methods:

NSW laboratory measles test data (2009–2012) were obtained from the Institute of Clinical Pathology and Medical Research (ICPMR), South Eastern Area Laboratory Services (SEALS) and Hunter Area Pathology Service (HAPS) in NSW. The number of negative episodes was collated and annual discard rates were calculated using mid-year population estimates from the Australian Bureau of Statistics.

Results:

From 2009 to 2012, the laboratory discard rate exceeded ≥ 2 non-measles cases per 100,000 population suggesting that adequate investigation occurred in NSW during this period. The rate appeared to increase over time which may be due to an increase of testing conducted or be reflective of the increase in cases over the 4-year period, including large outbreaks during 2011 and 2012 in the state.

Conclusions:

NSW laboratory discard rates are well above the target for measles elimination suggesting that high quality surveillance is occurring in the state. Our results will contribute to the calculation of a national discard rate to determine if Australia is meeting the criteria for high quality surveillance as a nation.

Prologue

My role

In April 2012, a number of discussions with experts in measles epidemiology around Australia and the DoHA, led to the formation of the Measles Elimination Working Party. I was most fortunate to be included in this working group, as during this time I had embarked on a number of measles related projects. The role of this working party is to provide technical expertise and evidence to the measles national verification committee who will assess Australia's measles elimination status. An essential criterion for the verification of measles elimination is high quality surveillance. One method to determine this is through measuring the number of suspected cases of measles that are ultimately confirmed to not be cases based on laboratory testing – known as discarded cases. To obtain a national rate of discarded measles cases, members of the working party were requested to obtain data from laboratories in their jurisdictions between 2009 and 2012. I was approached to be responsible for calculating the NSW laboratory discard rates, which I was keen to do as I had not previously worked with laboratory data and I saw this as an opportunity to analyse laboratory data for the first time. I accessed data from 2 laboratories; the Institute of Clinical Pathology and Medical Research (ICPMR) and South Eastern Area Laboratory Services (SEALS) and collated the results from these 2 laboratories with results from Hunter Area Pathology Service (HAPS) to calculate a state discard rate. David Durrheim was responsible for conducting the data analysis for HAPS and provided me with the results of his analysis.

Lessons learned

This project taught me a number of lessons that I am sure will help me in the future. Firstly, this was the first time that I was given data very much in its raw extracted form. There were many discrepancies in the data that I needed not only to clarify with laboratory staff but also needed to clean in SAS. It taught me that the process of data cleaning can take a long time, and in this instance, much longer than the actual calculation of the discard rate. As time-consuming as it may be however, I learnt how important data cleaning is to the validity of your results. In SAS, I learnt a number of new functions including: Proc Transpose, splitting your dataset into two (one with duplicates and one without) and recoding variables using new techniques. I also learnt the limitations inherent to laboratory data, particularly that it is difficult to ascertain whether individuals who are tested for IgM (without knowledge of whether they were tested for IgG) may in fact not be suspected cases but individuals being

screened for measles immunity. Another lesson learnt, was in regards to the type of laboratory test used. I learnt that the type of testing that is conducted by laboratories is very much based on the preference of the chief virologist and that test type varies within NSW. And what test type used is important as test results may be affected by the sensitivity and specificity of each test type used. I learnt that the best method to measure discard rate is to have additional information on each individual's clinical symptoms to ensure that the analysis did only include suspected cases of measles.

Public health action

The results of this project will be included into a national discard rate calculation as an indicator of the quality of measles surveillance in Australia. The discard rate will provide evidence as to whether measles elimination can be formally declared in Australia. This is the first time that a national discard rate has been calculated in Australia. Furthermore, this project is expected to be part of a publication of the national discard rate in the country.

Acknowledgements

First and foremost, I would like to thank Heather and Aditi for their guidance in developing SAS program used to conduct the analysis. Their patience and preparedness to impart their knowledge to me was incredibly kind. I am also most grateful to David Durrheim for his feedback on the methodology and results, providing his expertise to this project and his generosity in answering all my questions. This project could not have been done without the kindness and time spent by Juliana Iles-Mann and Terence Flood from Pathology West and Peter Robertson from SEALS who provided the data from ICPMR and SEALS and were kindly on hand to answer any questions I had. There was no incentive for them to be so forthcoming with help, yet they both were very wonderful in imparting their knowledge and time for this project. Additional thanks must also be given to Kenneth McPhie from ICPMR who provided us with advice.

Introduction

To verify the sustained elimination of measles in a country, a number of criteria need to be satisfied.⁵¹ This includes: the documentation that endemic measles transmission has not occurred in ≥ 36 months; the presence of a high quality surveillance system and the interruption of endemic measles through genotypic evidence.⁵¹ One indicator of high quality surveillance is achieving an annual reporting rate of ≥ 2 non-measles cases per 100,000 per population. Achieving this is suggestive that adequate investigation of suspected measles cases (i.e. individuals with measles-like-illness) is occurring and would be sufficient to detect an endemic strain of measles virus, if this was occurring. In Australia, information on suspected case investigations does not exist on the NNDSS. An alternative method to measure the reporting rate of suspected measles cases is through the use of laboratory data. Harpaz and Papania concluded that IgM testing in the United States was a valid index of measuring measles-like-illness incidence.¹²⁶ The author's posited a standard of at least 1 measles-like-illness case per 100,000 population to be used as a minimum standard rate of investigation.¹²⁶ In Australia, the rate of discarded non-measles cases has been calculated in Victoria; between 1998 and 2003, 72% of measles notifications were discarded following testing providing a median annual discard rate of 2.9 per 100,000 population.¹²⁷ The discard rate has never been calculated in NSW, the most populous state in Australia. The objectives of this study were to calculate the rate of discarded measles cases in NSW between 2009 and 2011 and assess whether the results met the minimum standard of case follow-up and laboratory testing.

Methods

NSW laboratory measles test data between 2009 and 2012 were obtained from the Institute of Clinical Pathology and Medical Research (ICPMR), South Eastern Area Laboratory Services (SEALS) and Hunter Area Pathology Service (HAPS) for the following test types: immunoglobulin M (IgM); immunoglobulin G (IgG; HAPS only and ICPMR in 2012); nucleic acid detection by Polymerase Chain Reaction (PCR) and; antigen detection by Immunofluorescence (IF). Other variables used in the analysis included a unique patient identifier, sex, postcode (ICPMR and HAPS), date of birth, specimen collection date and test result.

The three laboratories where data were obtained encompassed parts of metropolitan and regional NSW. ICPMR services hospitals and laboratories in western Sydney,¹²⁸ SEALS services all public hospitals in the South Eastern Sydney area and other private hospitals, laboratories and community-based GPs¹²⁹ and HAPS provides services to the Hunter New England area.¹³⁰

Exact duplicates (unique patient identifier, test type, specimen collection date and test result) were removed. If entries were duplicated by test type and specimen date but differed by test result, only the entry with a positive result was kept.

A temporary patient identifier was assigned to records where a unique patient identifier was missing; if sex, postcode (if available) and date of birth were identical to another record, the same temporary patient identifier was assigned.

Measles episodes were calculated and an episode of measles was defined as an event of suspected measles infection in an individual. An episode of suspected measles was considered the same if the specimen collection date was within 28 days of the earliest specimen collection date for the same unique patient identifier. Multiple test results were carefully scrutinised to determine whether they may have represented testing in the convalescent period. If the number of days between samples exceeded 28 days, episodes of suspected measles were considered different unless the first episode produced a positive result.

For ICPMR and SEALS data, only episodes involving PCR and/or IF tests were included in the analysis (**Table D-1**). For HAPS data, episodes not including PCR that

were IgM negative/ IgG positive or IgG equivocal were excluded from the analysis. These exclusions were conducted to prevent an overestimation of the discard rate due to the inclusion of individuals who might have been screened for immunity rather than being tested for suspected measles.

Table D-1. Tests used to define a measles episode by laboratory, NSW

| Laboratory | | |
|------------|------------------------|-------|
| ICPMR | HAPS | SEALS |
| PCR | PCR | PCR |
| IF | IgM+/IgG– IgM–/IgG– | IF |

A sensitivity analysis was also conducted on 2012 ICPMR data comparing negative test results using the two different inclusions of what an episode was (i.e. ICPMR/SEALS versus HAPS) , to determine if there was a difference in results.

A positive result from any test listed above (except IgG) was considered to be a positive episode whilst if all tests were negative the episode was considered negative. If a test result was equivocal, it was considered to be a negative result.

The year of specimen collection and the final result for each episode of suspected measles were used to calculate testing rates per population and positive measles rates. To calculate the rate of non-measles (discarded) cases by year, the sum of negative results from the three laboratories was divided by the NSW mid-year population estimate for the corresponding year. Mid-year population estimates were obtained from the Australian Bureau of Statistics. SAS and Microsoft Excel were used to clean the data and calculate rates, respectively.

Results

Between 2009 and 2012, there were 2188 suspected measles episodes tested at ICPMR with 56.5% (n=1236) of these episodes occurring in 2012 (**Table D-2**). Measles antigen detection by IF was the most common test used to diagnose a suspected measles episode, 92.8% of all tests used IF only.

Table D-2. Measles result by test type 2009–2012, ICPMR

| Test type | 2009 | | | 2010 | | | 2011 | | | 2012 | | |
|-----------|----------|----------|-------|----------|----------|-------|----------|----------|-------|----------|----------|-------|
| | negative | positive | Total | negative | positive | Total | negative | positive | Total | negative | positive | Total |
| IF only | 135 | 3 | 138 | 284 | 2 | 286 | 457 | 6 | 463 | 1123 | 21 | 1144 |
| PCR only | 0 | 0 | 0 | 1 | 0 | 1 | 3 | 1 | 4 | 1 | 0 | 1 |
| IF/IgM | 3 | 1 | 4 | 7 | 1 | 8 | 20 | 15 | 35 | 70 | 16 | 86 |
| IgMPCR | 0 | 0 | 0 | 1 | 0 | 1 | 3 | 0 | 3 | 3 | 1 | 4 |
| IF/PCR | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 2 | 0 | 0 | 0 |
| IF/IgMPCR | 0 | 0 | 0 | 0 | 1 | 1 | 5 | 1 | 6 | 1 | 0 | 1 |
| Total | 138 | 4 | 142 | 293 | 4 | 297 | 490 | 23 | 513 | 1198 | 38 | 1236 |

In contrast, there were 624 measles episodes tested between 2009 and 2012 at SEALS (**Table D-3**), of which 55% (n=343) of tests were conducted in 2012. The most common test used was a combination of IF and PCR tests, with 54% (n=335) of all episodes being tested with these two tests.

Table D-3. Measles result by test type 2009–2012, SEALS

| Test type | 2009 | | | 2010 | | | 2011 | | | 2012 | | |
|---------------|----------|----------|-------|----------|----------|-------|----------|----------|-------|----------|----------|-------|
| | negative | positive | Total | negative | positive | Total | negative | positive | Total | negative | positive | Total |
| IF only | 15 | 1 | 16 | 29 | 0 | 29 | 0 | 0 | 0 | 87 | 0 | 87 |
| PCR only | 0 | 0 | 0 | 8 | 1 | 9 | 8 | 2 | 10 | 24 | 4 | 28 |
| IF/IgM | 4 | 0 | 4 | 6 | 0 | 6 | 0 | 0 | 0 | 10 | 0 | 10 |
| IF/PCR | 0 | 0 | 0 | 31 | 1 | 32 | 99 | 16 | 115 | 139 | 49 | 188 |
| IgMPCR | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 2 |
| IF/IgM/CFT | 5 | 3 | 8 | 1 | 1 | 2 | 0 | 0 | 0 | 0 | 0 | 0 |
| IF/IgMPCR | 0 | 0 | 0 | 0 | 0 | 0 | 15 | 3 | 18 | 20 | 8 | 28 |
| IgMPCR/CFT | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 1 | 3 | 0 | 0 | 0 |
| IF/IgMPCR/CFT | 0 | 0 | 0 | 1 | 0 | 1 | 15 | 13 | 28 | 0 | 0 | 0 |
| Total | 24 | 4 | 28 | 76 | 3 | 79 | 139 | 35 | 174 | 281 | 62 | 343 |

Measles testing was lowest in HAPS (**Table D-4**) with 272 measles episodes during this period. Testing number by year did not appear as disparate as the other 2 laboratories with 32.3% (n=88) of tests occurring in 2012.

Table D-4. Total tests conducted and positive/negative results by laboratory 2009-2012*, NSW

| Year | ICPMR | | | SEALS | | | HAPS | | |
|------|-------------|----------|----------|-------------|----------|----------|-------------|----------|----------|
| | Total tests | Positive | Negative | Total tests | Positive | Negative | Total tests | Positive | Negative |
| 2009 | 142 | 4 | 138 | 28 | 4 | 24 | 44 | 2 | 42 |
| 2010 | 297 | 4 | 293 | 79 | 3 | 76 | 71 | 7 | 64 |
| 2011 | 513 | 23 | 490 | 174 | 35 | 139 | 69 | 2 | 67 |
| 2012 | 1236 | 38 | 1198 | 343 | 62 | 281 | 88 | 2 | 86 |

* Only including IF/PCR results except for HAPS which included IgM/IgG serology results (apart from those that were IgM - / + (or equivocal) IgG

Overall, in 2009–2012, the rate of negative measles cases (i.e. discard rate) remained above 2 non-measles cases per 100, 000 population in NSW (median= 7.9 per 100,000 population; range= 2.9–21.4 per 100,000 population) and, increased with year (**Table D-5**). The rate of measles cases also increased by year, with 14 cases per million population observed in 2012, ten times the rate observed in 2009 (1.4 cases per million). Testing rate also increased by year with 1667 tests conducted in 2012 (22.9 test per 100 000 population) compared to 214 tests in 2009 (3.0 per 100,000 population).

Table D-5. Measles testing, negative and positive rates for NSW by year, 2009-2012*

| | | Tests | | | Rates | | | |
|----------|------|-------------|----------|----------|------------|----------------------------|-----------------------------|-----------------------------|
| Location | Year | Total tests | Positive | Negative | Population | Testing Rate (per 100 000) | Positive Rate (per million) | Negative Rate (per 100 000) |
| NSW | 2009 | 214 | 10 | 204 | 7134421 | 3.0 | 1.4 | 2.9 |
| | 2010 | 447 | 14 | 433 | 7232589 | 6.2 | 1.9 | 6.0 |
| | 2011 | 756 | 60 | 696 | 7211468 | 10.5 | 8.3 | 9.7 |
| | 2012 | 1667 | 102 | 1565 | 7290345 | 22.9 | 14.0 | 21.4 |

* Only includes tests where a PCR and/or IF test was performed (ICPMR & SEALS), Includes IgM+/-IgG results except where IgM -/ + (or equivocal) IgG (HAPS)

The sensitivity analysis found that by using the inclusion criteria of episodes by test type from the HAPS methods, 157 more negative test results were captured from this method compared to the inclusion criteria used for episodes in the ICPMR/SEALS methods (Table D-6)

Table D-6. Sensitivity analysis on measles result by test type using ICPMR/SEALS versus HAPS methods, ICPMR 2012 data^

| Test type | Final Result (ICPMR/SEALS method) | | | Final Result (HAPS method) | | |
|-------------|-----------------------------------|----------|----------|----------------------------|----------|-------|
| | negative | positive | Total | negative | positive | Total |
| IF only | 1122 | 21 | 1143 | 1122 | 21 | 1143 |
| PCR only | 1 | 0 | 1 | 1 | 0 | 1 |
| IgM only | excluded | excluded | excluded | 144 | 2 | 146 |
| IgM/IgG^ | excluded | excluded | excluded | 13 | 7 | 20 |
| IgM/PCR | 1 | 0 | 1 | 1 | 0 | 1 |
| IF/IgG | 1 | 0 | 1 | 1 | 0 | 1 |
| IF/IgM | 34 | 10 | 44 | 34 | 10 | 44 |
| IF/IgM/IgG | 36 | 6 | 42 | 36 | 6 | 42 |
| IF/IgM/PCR | 1 | 0 | 1 | 1 | 0 | 1 |
| IgM/PCR/IgG | 2 | 1 | 3 | 2 | 1 | 3 |
| Total | 1198 | 38 | 1236 | 1355 | 47 | 1402 |

^ Only IgM-ve/ IgG-ve and IgM+ve/IgG-ve were included in the analysis
The only difference between HAPS and ICPMR methods to obtain negative tests were 157 more discard cases for the HAPS methods which included IgM only and IgM/IgG tests.

Discussion

Our results provide evidence that NSW met the minimum discard rate ≥ 2 non-measles cases per 100,000 population⁵¹ for the years 2009–2012. This suggests that adequate measles surveillance is occurring in NSW, and will contribute to the national measles discard rate calculation to assess the national adequacy of surveillance; an essential criteria for the verification of measles elimination.⁵¹

The calculation of a measles discard rate to assess the performance of a surveillance system was first proposed in 2004.¹²⁶ The authors' recommended minimum standard of one discarded case per 100 000 population per year was applied in Victoria, where the enhanced surveillance system was found to exceed the minimum standard. Between 1998 and 2003, the annual discard rate was consistently ≥ 2 cases per 100,000 population. Our results are in line with the Victorian study, the only known published Australian study to have used discard rates to assess the quality of measles surveillance.¹²⁷ A similarity between the two studies which also had been noted globally,^{121, 124} was the increase in the discard rate during epidemics. During 2011 and 2012 the testing of suspected measles cases in NSW increased. This is likely to be due to heightened awareness among clinicians when an individual presents with measles like illness; as supported by Harpaz and Papania¹²⁴ resulting in more suspected measles cases being tested and subsequently an increase in non-measles discard rates.

A number of limitations to this study must be noted. Firstly, our results for New South Wales excluded measles testing from private laboratories. It is not known what proportion of measles diagnostic testing is conducted in private versus public laboratories. We however, used the entire NSW population estimate as the denominator whilst the numerator included three public laboratories. This calculation was an underestimate of the true discard rate. Despite this underestimation, our results exceeded the minimum requirement of ≥ 2 non-measles cases per 100,000 population providing strong evidence that NSW has high quality surveillance, with suspicion high enough to detect a wild strain of measles, if it was circulating in the state.

Additionally, diagnostic tests conducted differed by laboratory. As the sensitivity and specificity of tests differ, particularly depending on the stage of disease, this might limit the validity of our results. For example, ICPMR primarily used IF as their diagnostic test

for measles. The sensitivity of IF has been suggested to be 50—60%. This has the potential to overestimate the discard rate as true positive cases may be classified as a negative result. Our results indicate that most suspected cases only have an IF test conducted. Given the low sensitivity, recommendations should be in place that an alternative test such as PCR is conducted (based on its high sensitivity and specificity) or a number of different tests to increase the sensitivity of detecting a true measles case. More standardised routine testing procedures state-wide would also increase the validity of the discard rates.

A strength of the study is that attempts were made to minimise the overestimate of negative cases through the conservative approach to what tests were included in our analysis. Firstly, an episode of measles was only included in our analysis if an IF or PCR test was conducted. Data were not collected on IgG testing during from ICPMR (2009-2011) and SEALS (2009-2012). Concerns were raised that if the IgM results were included in the analysis, it may overestimate the discard date as IgM testing may have been conducted as a concurrent test for immunity screening (IgG) rather than testing due to a suspected measles case. It was therefore important that these tests were not included in our analysis. Moreover, an episode of measles was only included in the HAPS analysis if the individual had a PCR test or was IgG-ve/IgM+ve or IgG-ve/IgM-ve. This again was a conservative approach, trying to account for immunity screening. This method however, would include individuals tested for immunity who were found to be susceptible (i.e. IgG-ve/IgM-ve), potentially overestimating measles discard rate. We conducted a sensitivity analysis to determine how our results would change given the two different inclusion criteria we had for ICPMR/SEALS versus HAPS data. Our results identified that the inclusion criteria for ICPMR/SEALS data was more conservative, providing a lower number of negative measles cases and subsequently a lower measles discard rate. Despite this conservative approach, the negative discard rate for NSW in 2012 was still well above the minimum threshold with 21.4 non-measles cases per 100,000 population.

Additionally, using laboratory non-measles discard rates as a measure of the adequacy of a surveillance system in itself has a number of challenges. Firstly, it is well documented that in regions where measles is rare, clinicians may not suspect measles.¹³¹ Low suspicion and the subsequent non-referral for a measles test will affect not only testing rates but also non-measles discard rates. This limitation has

been described previously.¹²⁷ Despite this, during 2009–2012, our rates far exceeded the minimum standard of ≥ 2 non measles cases per 100,000 population.

There has been previous discussion on whether caution is required when measuring the quality of surveillance using measles discard rates. Suspect measles cases may vary largely by region and are dependent on, among other things the local epidemiology of measles like illness. Such large variation makes establishing a minimum reference standard challenging and suggestions have been made that a reference standard be dependent on the region of a country.¹³² However, the minimum standard of ≥ 1 non-measles case per 100,000 population was intended not to measure the sensitivity of a surveillance system but rather, identify whether a surveillance system was weak.¹³³ Indeed, it is important to note that the calculation of a discard rate is not a sole measure to quantify the performance of a surveillance system. More recently, other indicators for high quality surveillance have been included to assist countries in assessing this. These include: the timeliness and representativeness of reporting; the proportion of suspected cases with a specimen collected to be tested in an accredited laboratory; the proportion of laboratory confirmed outbreaks with adequate samples submitted for viral detection; and the adequacy of investigation within 48 hours of notification.⁵¹

Conclusions

The calculation of laboratory discard rates is an important component in measuring the quality of measles surveillance. Our results provide evidence that since 2009, New South Wales has achieved and surpassed the minimum standard of ≥ 2 non-measles cases per 100,000 population and in turn, surveillance would likely detect endemic measles if it was circulating in the state. A national measles discard rate will be calculated, incorporating our results for NSW, which subsequently will contribute to the evidence submitted to assess the verification of measles in Australia.

SECTION 2

Public Health Action Group: A group of
professionals in New South Wales
who are working to improve the health
of the community.

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SECTION E

Public health action during a measles outbreak in New South Wales

“For the things we have to learn before we can do them, we learn by doing them.”

– Aristotle

Challenges in identifying a source of measles transmission in an emergency department

Abstract

Background:

At the beginning of the 2012 NSW measles outbreak, four cases, of which three were infants too young to be immunised, were notified to health authorities in metropolitan Sydney. All had attended a tertiary paediatric hospital ED on 11 May 2012; however, a source case had not been identified. The objective of this project was to identify the source of the four measles cases.

Methods:

An algorithm to detect the suspect source case was developed and comprised of reviewing patient notes of all children who had attended the ED on 11 May 2012. Patients were assessed by time and symptom presentation. Vaccination status was obtained, (where possible) from the Australia Childhood Immunisation Register (ACIR). A suspect source case was defined as any patient that presented with fever and other symptoms consistent with measles (cough, coryza, conjunctivitis or rash) that were unvaccinated or partially vaccinated for measles. A questionnaire was developed and the parents of suspect cases interview over the phone.

Results:

There were 162 patients that presented to the ED on 11 May. The medical notes of 40 patients were reviewed and eight febrile suspect cases were identified of which three were excluded based on alternative diagnoses. From parent interviews, none of the five suspect source cases identified were found to be the source case.

Conclusions:

This outbreak highlighted the challenges of identifying the source of measles and also provided further evidence of infants' susceptibility to measles using a non-validated algorithm. As healthcare associated transmissions increasingly become common in an era of measles elimination, this algorithm the potential to be further developed and used in identifying a source case of measles if a similar scenario is to occur in the future.

Prologue

My role

In 2012, during May, four cases of measles were notified to the Western Sydney Public Health Unit (PHU) within a four-day period. Following case investigations, all four cases were linked by time and place to an ED at a paediatric teaching hospital in Sydney. Dr Vicky Sheppeard, the manager of the PHU approached Alexis (my fellow MAE colleague at NCIRS) and I to investigate the source of the four cases. Our role was to liaise with ED staff, examine ED charts, develop a questionnaire and interview suspect source cases to try to identify the index case. Alexis and I communicated our findings at a weekly Infectious Disease Meeting at the paediatric hospital and also for Journal Club at NCIRS. Additionally, we wrote a report of our findings for dissemination to the PHU and ED within two months of the investigation commencing to document the incident, the investigation that occurred and lessons learned that may reduce measles cases in the future in this setting.

Lessons learned

There were abundant lessons to be learned during this project. Most notably that despite all efforts to attempt to identify a cause or source, you can be unsuccessful. It was challenging to interview parents of patients who we suspected may be the index case without explicitly inferring anything that may upset the parents. I learnt that when communicating with parents, it is important to listen to their concerns, be clear in getting your message across and ask questions in a sensitive manner.

At times, Alexis and I were unsure of how to go about conducting the investigation and what the next steps should be. We were fortunate that during this investigation we had access to experienced public health experts who had a wealth of experience in measles outbreaks who provided guidance and advice. One thing that I believe we could have done better was documenting all stages of the investigation and organising records more systematically to be more efficient. Upon reflection, I realised that this was a weakness of the project and put this into practice for the MAE projects subsequent to the outbreak investigation.

The ED staff displayed a wealth of knowledge and it made me realise that you should take advantage of their experience and ask any questions you may have. They related

to me that there were many unrecorded people in the ED including wards persons, visitors and family members and were forthcoming in informing us of the challenges of what we were trying to do i.e. that we would have difficulty in contacting every individual that had passed through the ED on that day.

Public health action

Unfortunately we were unable to find the source of infection at the paediatric hospital. It highlighted though the challenges in trying to identify a source case and also indicated that with current procedures it is difficult to monitor the movements of every individual present in the ED ward. Our report may impact future ED practice on infection control including the documentation of individuals that enter the ED.

Acknowledgements

I am most thankful to Vicky for giving Alexis and I the opportunity to be involved in this project and putting her trust in us. I feel very fortunate to be able to work alongside another MAE and at times, although I was uncertain during many stages of this project she was a great support person and advisor. Samantha Mihailovich (Nursing Unit Manager of Emergency) and Dr Mary McCaskill (Director of Emergency) were incredibly generous with all their knowledge and happily answered all the questions we had. Many thanks go to Samantha for taking time out of her busy schedule to give us a tour of the ED. Lastly, I am most grateful to NCIRS and my field supervisor Aditi for allowing me the time to conduct this project.

Introduction

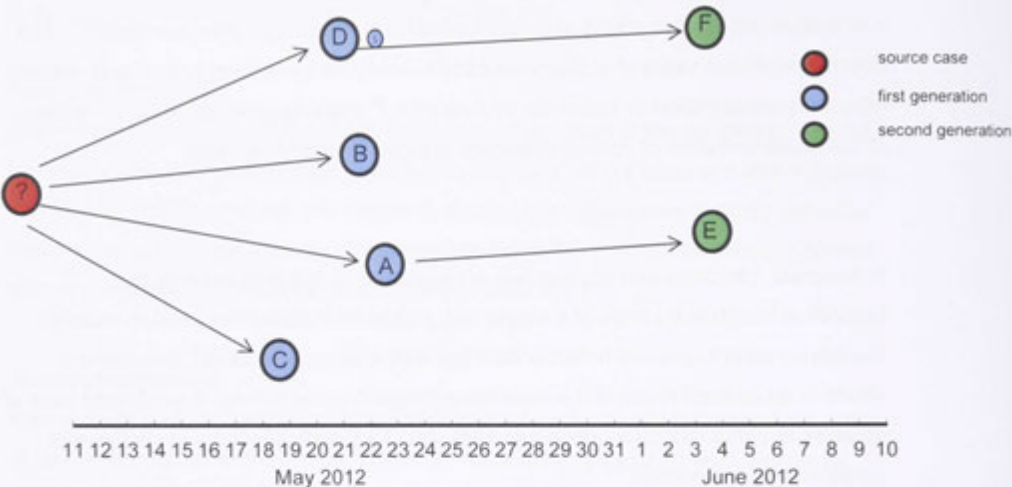
In countries where measles is a rare condition, transmission of the virus often occurs in healthcare settings, usually crowded and busy environments frequented by those most susceptible; infants too young to be immunised and the immunocompromised.¹³¹ The positive predictive value of a diagnosis based on clinical symptoms is low and without laboratory confirmation or suspicion by clinicians,¹⁶ misdiagnosis can lead to the delay of the implementation of control strategies to prevent further infection.

In Australia, clinicians and laboratories are legislatively required to notify their respective health authorities of a suspected, probable or confirmed case of measles. Guidelines exist to provide health authorities with a protocol to assist containment efforts in an attempt to prevent a measles outbreak from occurring. A confirmed case of measles requires laboratory definitive evidence of measles infection, or clinical and epidemiological evidence.⁹⁸

Although there has been a drastic reduction of measles over the past two decades, a number of outbreaks have occurred in recent times, most notably the 2012 outbreak in New South Wales (NSW). This outbreak was the largest outbreak to have occurred in fifteen years, and, since measles elimination was reported to have been achieved in Australia⁶. The index case was a 25 year old Australian-born male who had returned to Australia from a trip to Thailand in April 2012. There were 168 cases identified, of which the last case had symptom onset during November 2012. Most cases were from western and south-western Sydney. Transmission by this individual resulted in three known secondary cases and molecular genotyping identified the strain to be D8.

A month later, four cases of measles (Cases A, B, C and D) were notified to two public health units (Western Sydney and Northern Sydney) within a six-day period. (**Figure E-1**).

Figure E-1 Chain of transmission by date of onset following likely exposure at a Sydney paediatric hospital, May 2012



Upon further investigations, it was revealed that within the incubation period, all four cases had presented or accompanied a sibling to the ED of a large paediatric hospital at around the same time on 11 May 2012. Of the four cases, three were too young to have been vaccinated (Cases A, B and C; range: 7–11 months old). The remaining case (Case D) was a 17 year old girl with no record of receipt of measles vaccination (**Table E-1**). Case B was exposed to a sporadic case of measles within his incubation period and had been contacted for this exposure however the genotype of this case was later identified as B3.

Table E-1. Time spent by secondary measles cases in the Sydney paediatric hospital ED, 2012

| Case | Sex | Age | Estimated arrival time at ED | Discharge time |
|--------|--------|-----------|------------------------------|-----------------|
| Case D | Female | 17 years | 14:45 | 01:40(next day) |
| Case C | Female | 10 months | 17:40 | 21:19 |
| Case A | Female | 11 months | 17:55 | 21:37 |
| Case B | Male | 7 months | 20:55 | 23:54 |

Specimens from Case A and Case C were transferred to the Victorian Infectious Diseases Reference Laboratory (VIDRL) for genotyping and both returned genotype D8. No genotype specimens were available for Case B and Case D. The only other known measles cases with a D8 genotype in NSW at the time was the 25-year old index case and the three secondary cases identified a month earlier. The four nosocomial acquired cases were assumed to have been linked to the index case based on identical genotypes, time and place. This assumption was made due to the rareness of measles in Australia and the only other confirmed cases during this period, being a case with genotype B3). The paediatric hospital was located within the same local health district (LHD) as the residence of the index and secondary cases. The aim of this study was to identify the source case that presented to the ED on 11 May 2012 and to report on the methodology used in an attempt to identify the source of infection.

Methods

The algorithm

An electronic list of all ED attendances for 11 May 2012 which included Medical Record Number (MRN), date of birth, times of arrival, triage and departure and summary of presenting problem was provided by the ED director. Electronic ED patient notes were used to gather information on presenting condition, medical history, provisional diagnosis at time of discharge and whether transfer as an in-patient occurred. The Australian Childhood Immunisation Register (ACIR) was consulted for individuals' immunisation status when appropriate.

Following the provision of the list of ED attendances, an algorithm was developed to identify the source case by time, place and person (symptom presentation and vaccination status). The development of the algorithm was aided by the national outbreak guidelines and documented symptoms of measles.^{12, 19} The complete list of attendees at the ED for 11 May was reviewed by time of arrival and departure. Current national protocols stipulate that contacts be followed up for up to 2 hours after the index case has departed.¹³⁴ Thus, the time range of exposure to measles was estimated to be 2 hours before the last case arrived in the ED waiting room and one and a half hours after the first secondary case was discharged from the ED (i.e. 18:55 to 22:49). On average, patients waited an hour and a half in the waiting room before the time of arrival is entered into the electronic ED patient notes (personal communication, ED director) and hence all patients were given an estimated arrival time one and a half hours before the entered time of arrival in patient notes. The complete list of attendees was further restricted by presenting condition. Patients who presented with trauma, mental health issues, central nervous system, urological symptoms, constipation, appendicitis, routine childhood examination and dental concerns were excluded.

Having excluded children who did not fit the timeframe detailed above or those whose conditions were not compatible with measles, review of the remaining patients by symptoms recorded in hospital notes and immunisation status from ACIR was conducted. Suspect cases were defined as any patient that presented with fever and other symptoms consistent with measles (cough, coryza, conjunctivitis or rash) who were unvaccinated or partially vaccinated for measles. Children listed as 'did not wait' were reviewed by immunisation status and symptoms and if no information was

present, their parents were contacted for an interview. We developed a questionnaire (Appendix) to gather information about the patient's symptoms, recovery, vaccination status, movements in the ED to determine whether or not they might be the source case.

Additionally, in an attempt to determine whether a more precise location of exposure within the ED could be determined, attempts to recreate the movements of cases within the ED using ED notes, an ED map and the hospital's official incident report occurred. The hospital's official incident report was an internal document that compiled information supplied to the Infection Control Team which was circulated to a number of staff members and public health unit staff including paediatricians, infectious disease specialists and occupation health and safety staff. It outlined the event and the action taken by Infection Control at the hospital.

Results

General public health response

Following receipt of the four notifications, control measures for each confirmed case were implemented as per national guidelines.¹⁹ Interviews with parents of cases were conducted by public health unit staff and a number of settings were identified where cases may have potentially exposed individuals during their infectious period. This included household members; in-patients who had been in the same ward as cases; contacts from the ED and medical centre waiting rooms, schools and retail outlets.

Public Health Unit and surge staff conducted contact tracing to assess the risk of infection of individuals exposed; determine current health and vaccination status; recommend and explain interventions and detail appropriate actions required upon becoming symptomatic. Measles fact sheets were emailed or posted to provide additional information. In total, 270 individuals were contacted; either through a phone interview to determine their risk and provide advice or if individuals were unable to be contacted, a letter was posted to their address.

Post Exposure Prophylaxis (PEP) clinics were held due to the high number of susceptible individuals exposed at the paediatric hospital ED by three of the four cases (Cases A, B and D). Prophylaxis administered at the clinic included Measles, Mumps, Rubella (MMR) vaccine or Normal Human Immunoglobulin (NHIG). Each individual was reviewed using post exposure guidelines to determine the appropriate prophylaxis to be administered.¹³⁴ Overall, 18 individuals were administered NHIG and 8 individuals received MMR.

As an additional control measure, public health alerts were issued to the paediatric hospital staff, general practitioners in the area and media outlets warning measles occurring (Appendix).

Investigation to identify the source case

ED staff had conducted preliminary investigations to identify the source of infection shortly after establishing the link of the four cases to the ED. However, their efforts were unsuccessful and we were requested to conduct a comprehensive investigation following the completion of control measures

Figure E-2 shows the steps used to try to identify the source case. There were 162 children who presented to the ED on 11 May 2012 (Figure E-2) of which we excluded 92 due to the timing of their presentations.

Figure E-2. Algorithm to identify suspect source measles case presenting at a Sydney paediatric hospital ED, 11 May 2012



Based on guidelines followed,¹³⁴ individuals were included as possible source cases if they were discharged two hours (18:55) before the last case (Case D) arrived at 20:55 and if they arrived in the ED waiting room one and a half hours (22:49) after the first case (Case C) was discharged at 21:19 (Figure E-3).

Figure E-3.Overlap times of secondary measles cases and time that source case must have been present in the Sydney paediatric hospital ED, 2012

| | 11-May | | | | | | | | | | | | 12-May |
|--------|---------|---------|---------|---------|---------|---------|---------|---------|---------|----------|----------|----------|---------|
| | 1:00 PM | 2:00 PM | 3:00 PM | 4:00 PM | 5:00 PM | 6:00 PM | 7:00 PM | 8:00 PM | 9:00 PM | 10:00 PM | 11:00 PM | 12:00 AM | 1:00 AM |
| Case A | | | | | | | | | | | | | |
| Case B | | | | | | | | | | | | | |
| Case C | | | | | | | | | | | | | |
| Case D | | | | | | | | | | | | | |
| ? | | | | | | | | | | | | | |

The four confirmed measles cases (Cases A, B, C and D) were also excluded resulting in 66 remaining children. Additionally, we excluded 17 children who presented with conditions which were incompatible with measles (i.e. patients who presented with trauma, mental health issues, central nervous system, urological symptoms, constipation, appendicitis, routine childhood examination and dental concerns). And nine patients who did not wait: 3 fully immunised patients, 3 afebrile patients and 3 patients who presented with symptoms unrelated to measles (n=2 trauma, n=1 blood in stool) were also excluded.

We reviewed ED medical charts for the remaining 40 patients. Of these, a number of patients were excluded as they were afebrile (n=17); had received 2 doses of MMR (n=9); or had a definitive diagnosis of a non-measles condition (typhoid fever or *Salmonella* serotype Enteritidis (n=2); allergic reaction (n=1);) were followed up by ED staff and not considered suspect cases (n=2); and had suffered a febrile convulsion following vaccination (n=1). One patient was admitted as an in-patient following ED presentation and treated for suspected meningococcal septicaemia (PCR negative for *Neisseria meningitides* but urine culture positive for enterococcus species) thus was excluded

We conducted phone interviews with parents of 5 suspect source cases (**Table E-2**). The median age of suspect index cases was 17 months (range: 9 months–7 years). All 5 patients were reported to have recovered soon after presentation. One patient had previously been exposed to a sporadic case of measles at a local medical centre; however, this case was later identified as genotype B3.

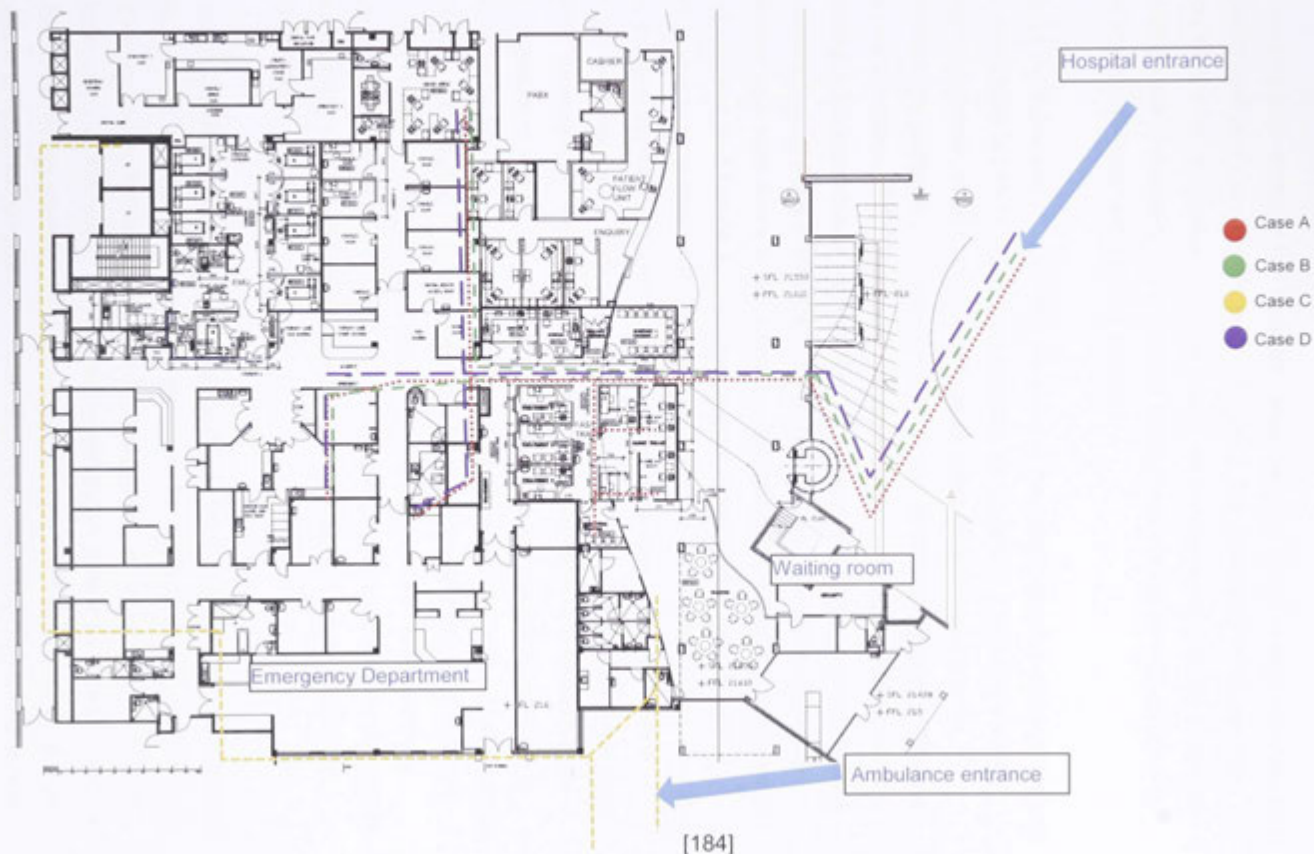
Table E-2. Demographics and symptoms of suspect source measles cases in the Sydney paediatric hospital ED, 2012

| Case | Age | Sex | Symptoms | Vaccination status | Other comments |
|--------------------|-----|--------|--|-----------------------------------|--|
| Suspect case one | 16m | Female | Coryza, fever, cough, otitis media, rash on face. | MMR1 | Exposed to measles genotype B3 7 May 2012 at a medical centre. Received antibiotics at CHW and parents reported improvement soon after. No new symptoms or ill household contacts. |
| Suspect case two | 10m | Female | Fever, cough, coryza. | Ineligible | Patient recovered soon after attendance at ED. Also attended GP after ED presentation. Ongoing itchy scalp. Represented 25 May with same symptoms. |
| Suspect case three | 7y | Female | Rash, fever, cough, possible conjunctivitis. | Unknown- later identified as MMR2 | Patient was ill for 1–2 days and diagnosed with flu. No household contacts had prior or post-illness. Parents' state fully vaccinated. |
| Suspect case four | 4y | Female | Fever and vomiting, diagnosed with a Urinary Tract Infection (UTI) | No record | Patient was diagnosed with UTI and did not acquire any new symptoms. No household contacts had prior or post-illness. |
| Suspect case five | 9m | Male | Fever, cough, coryza, vomiting and diarrhoea | Ineligible | Patient was not prescribed any medications post presentation and recovered soon after discharge. No household contacts had prior or post-illness. |

Following a review of the 5 cases with colleagues and the manager of communicable diseases at the western Sydney LHD, it was concluded that the five suspected source cases were unlikely to have been measles considering their recovery time occurred soon after discharge. Three of the five suspect cases were not observed to experience rash. Although suspect case one had a rash on her face, it reportedly did not spread to her torso or extremities. Due to unknown reason, ascertainment of the vaccination status of suspect case three was not recorded during preliminary investigations on ACIR, and her parents were interviewed. Their report of her vaccination status was later verified on ACIR.

Cases A, B and D had waited in the ED waiting room for approximately one and a half hours before being examined by ED staff (**Figure E-4**). The remaining case (Case C) was brought in by ambulance using an alternative entrance. It is not known how long children sat in the waiting room to how long they were in cubicles or rooms being assessed. Three of the cases (Cases A, B and D) have near identical movements around the ED whilst Case C was completely different. Based on these four cases' movements however, it is likely that the source case entered into the ED to have transmitted face-to-face to Case C. It is difficult to ascertain where transmission was most likely for each case; considering the source case could have been moved around the ED. Given the varying times of arrival to ED by Cases A, B and D; it is unlikely that all three occurred in the waiting room. Case C would most likely have acquired measles in the ward area where she was located before being moved to a ward external from the ED.

Figure E-4 Recreation of movements by the 4 secondary cases in the Sydney paediatric hospital ED, 11 May 2012



Discussion

We investigated a cluster of four measles cases that were linked by time and place to a paediatric emergency department on 11 May 2012. We developed an algorithm to identify the source of infection and even though we were unable to identify the source case during this investigation, our algorithm may be improved upon and validated to assist future outbreaks with a similar scenario.

Although the focus was on identifying the index of the case, this event also emphasised the susceptibility of infants in acquiring measles, particularly in a healthcare setting. During the outbreak, three of the four secondary cases were too young to be immunised, the youngest being seven months of age. Susceptibility among infants is not a new observation^{25, 26, 125}; however it suggests that more focus needs to occur in preventing such transmission. Though there have been suggestions to move forward the primary dose of MMR to less than 12 months^{25, 135}, seroconversion of measles antibodies have been found to be highest in older infants (> 15 months) compared to younger infants (9–11 months).¹³⁶ Further, a more recent study found vaccine effectiveness to be greater at 15 months compared to 12–14 months.¹³⁷ The immaturity of the humoral immune response in young infants, particularly those less than 6 months²⁷ indicates the complex nature in identifying the optimal time for the first dose of MMR. Vaccination of infants 9–11 months of age is currently only recommended when exposure to an infectious case has occurred.¹³⁴ A more practical approach in ensuring protection to infants in healthcare settings is perhaps to focus on establishing an isolation room during periods of outbreaks for all individuals presenting with fever and rash. Measles notifications had begun in the local health district the previous month, and heightened awareness by ED in containing suspicious measles cases may have prevented transmission, this however, will be discussed in more detail in the below project.

Our failure to identify the source case may be due to the limitations of our investigation. Firstly, the algorithm used was based on the use of ED notes. The validity of ED notes is not known and to my knowledge, no publications exist on measuring the validity of this information for this type of public health investigation. It must be stressed however that ED notes are not intended as a data source for epidemiological studies, its main purpose is to document clinical information of patients. Information on time of arrival and departure, signs and symptoms, temperature, location treated and diagnosis are of

utmost importance in applying this algorithm and if even one variable is not accurately captured the true index case of measles may have been missed. For example, the reliability of recording temperature or stating whether a patient was febrile in the electronic ED notes was not known. Seventeen patients were excluded based on being afebrile; had one of these in fact been febrile it is possible that further investigation would have revealed that they were the index case. Data are entered by qualified nursing or medical staff which makes error improbable but errors can occur. ED notes have the potential to play an important role in identifying index cases in infectious disease outbreaks believed to be transmitted in the ED and while it would be ideal to validate ED notes for this type of public health investigation how this could be done (given the variability between and within persons that also may be influenced by time of day or level of activity in the ED) as well the usefulness of doing this in the overall scheme of patient management needs to be considered.

A more pragmatic approach would be to validate the measles-specific algorithm itself. It was unfortunate that we did not validate the algorithm during the investigation due to time constraints. This was the first time that the algorithm developed was used we are unaware of existing algorithms to identify a source case in the past. We were however, guided by contact tracing guidelines and known symptoms of measles whilst developing the algorithm.

The first stage of excluding cases was by the time frame of likely measles transmission using current national protocols that recommend contacts be followed up for up to two hours after the index case has departed.¹⁹ Since the index case was unknown, all patients who presented two hours before the last case arrived in the ED waiting room and one and a half hours after the earliest case was discharged from ED were included, with the remaining patients on the list excluded. As highlighted in the next report of this thesis, there has been much discussion of the likelihood of transmission of measles two hours after the departure of an infectious case. The timeframe in this algorithm is conservative as it includes the possibility of lingering aerosols. Previous outbreaks in Australia,¹³⁸ including this outbreak (described in more detail in the next report) have generally found measles transmission in healthcare facilities to have occurred when both the index case and secondary case were present in the facility at the same time. Hence it is likely that based on time, the algorithm would have captured the true index case, if they were a person that attended the ED.

Another important consideration that may have assisted in identifying the index case is if the movements of all patients whilst in the ED were known. Movement of patients in the ED of the four secondary cases (Cases A, B, C and D) were collected in an incident report based on information collected for Infection Control. However, in the remaining patients that had attended the ED during this time, there was narrative text entered in some of them of their location however it varied considerably. In some countries like the United Kingdom, contact tracing is based on whether an individual was present in the same room as an infectious case of measles.¹³⁹ Given that the risk of measles transmissions in susceptible individuals is greatest when direct exposure occurs, it would have been useful if ED notes were able to capture the location and time of patients in the ED and indicate any movements within the ED and potentially incorporate this into the algorithm.

In the above discussion, time and place have been addressed in identifying the index case, and it was also important to exclude patients on the ED list by their signs and symptoms. After excluding potential source cases by time, symptom presentation was examined. A summary of the presentation problem was used (provided by the Director of ED) due to time constraints to review in-depth narrative text in ED notes to exclude patients by symptom presentation. Patients discarded were recorded as having an acute problem (such as trauma injury) which was completely unrelated to measles and thus unlikely to be the index case but possibly may have been during pre-prodrome.

Clearly use of symptom presentation in the development of an algorithm is an important factor in attempting to identify the index case of the outbreak. In some instances though, excluding by symptoms may not capture the index case if they happen to be pre-prodrome or a sub-clinical measles case. In some instances, partial immunisation can result in sub-clinical infection where symptoms are milder and may or may not include fever.¹⁴⁰ Even in fully vaccinated individuals, there is a possibility that measles infection can occur.¹⁴¹ Siblings exposed to measles on an aeroplane became infected despite records indicating they received 2 doses of MMR. Vaccine administration occurred at different times suggesting that it was not a cold chain issue or defective batch but possibly a genetic issue.¹⁴¹ If the true index case presented without fever, our algorithm would have excluded them, however, it is highly unlikely that a sub-clinical case of measles was the source of infection as there have been no reports of measles transmission to household contacts by subclinical measles cases.¹⁴⁰

Moreover, transmission may have occurred one day prior to prodrome¹² of a patient who presented to the ED with trauma or a problem not measles related. Given the time constraints of this investigation, we were unable to thoroughly review these patients. Following recommendations by clinicians and public health experts, we focussed on patients that had presented to the ED with a fever. We do not believe that any of these cases were the source case based on subsequent measles cases over the next few months that did not come from families known to have attended the ED on 11 May (other than the 4 confirmed cases identified).

Rather than a sub-clinical case being responsible for this measles outbreak, it is highly possible that the index case was not a patient presenting to the ED but an individual accompanying a patient or a hospital worker. The ED does not record visitors that enter the ED or non-medical staff such as ward persons that enter the ED. Given that hospital workers have been reported to continue working whilst infectious with measles⁹¹, it is a possibility that a worker was the source case. In 2007, however, the NSW Department of Health (now the Ministry of Health) issued a policy directive requiring health facility staff (newly recruited and existing) and students to be vaccinated against certain vaccine preventable diseases including measles, (unless they have been screened and found to be protected against measles).⁸⁶ How much this policy is adhered to is unknown, however the existence of a mandatory policy suggests that a hospital worker was less likely to be the source case. On the other hand, an individual accompanying a patient may indeed have been the source case; however there was no way to assess this as no records are taken of individuals entering the ED other than patients. Therefore one recommendation would be that all individuals accompanying an ill individual are recorded in the ED notes and a log book exists to collect information of all hospital workers that enter into the ED. This would not only be of benefit when attempting to identify a source case but would also come in useful during contact tracing if an individual with an infectious disease exposed others in the ED. Whilst this would be useful for public health, it may be difficult to implement in a busy ED setting which needs to be considered.

To this point, it is clear that many factors need to be taken into account in developing an algorithm to identify an index case of measles in a healthcare facility. Time, place and symptom presentation were used, and although the algorithm was guided by existing measles literature, it proved unsuccessful in identifying the index case. Despite this, the algorithm can serve as a guide for others to use and improve on, particularly

given the importance of healthcare transmissions during measles outbreaks that will be mentioned in more detail in the second part of this section.

Further studies on validating a refined version of the algorithm would assist in identifying an index case if a similar situation was to occur in the future. One example could be to apply the algorithm to past outbreaks that have occurred in a healthcare facility with a known index case and determine whether following the algorithm, that the index case would have been identified.

After following the algorithm, five interviews were conducted with suspected source cases. Interviews were conducted up to six weeks after the suspected transmission event date. Of the five suspect index cases, four were contacted within two weeks of the transmission event whilst it took five attempts of contacting the parent of one suspect case before an interview could be conducted (six weeks later). This is likely to have led to difficulty in recollecting the event by the parent of the one suspected case. However, it was assumed that having a child present to an ED would be traumatic and stressful for parents and hence resulted in remembering the event well. It is also noteworthy to mention that parents may have been concerned that their child was a 'suspected' source of measles. Their responses to the questionnaire may have reflected this however we drafted our questionnaire to not suggest or implicate individuals as the source of infection during interviews.

Conclusions

Though Australian measles vaccination coverage rates are high¹⁴², EDs are an important transmission setting for measles, particularly in infants. Healthcare setting transmission has been a common characteristic of recent measles outbreaks in developed countries and presents an obstacle to securing and maintaining measles elimination.^{47, 131, 143-146} The investigation of four cases of measles identified on 1 day from a Paediatric Emergency Department was unsuccessful in identifying the source of infection; which may have been due to using a non-validated algorithm. As healthcare settings are considered the predominant mode of transmission in countries where measles is rare, developing a validated algorithm to identify an index case would be useful to guide healthcare facilities in identifying an unknown index case of measles. The algorithm developed in this investigation serves as a guide to be used in the future to refine and validate an algorithm that has the potential to be applied in healthcare settings.

***The changing epidemiology of measles in an era of elimination:
Lessons from healthcare setting transmissions of measles
during an outbreak in Australia, 2012***

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Late draft manuscript– revisions required

Abstract

Background:

Increasingly, healthcare facilities are becoming common settings for measles transmission in countries where elimination has occurred. In 2012, seven years after measles elimination was reported in Australia, the country experienced its largest measles outbreak in 15 years. Indeed, a high proportion of cases in this outbreak were healthcare acquired. The objective of the study was to highlight key characteristics of healthcare acquired cases and in a post-elimination setting, consider whether the epidemiology of measles may be changing.

Methods:

A healthcare-acquired measles case was defined as a confirmed case April–November 2012 who had a coincident attendance with a measles-infected individual (source case) at a healthcare facility 7–18 days before symptom onset. We conducted descriptive analyses using case series data from the metropolitan Sydney region to examine demographic characteristics, including age, sex, vaccination status and the time of presentation. The number of presentations, time of presentation, symptoms upon presentation and isolation information were obtained for source cases. The number of contacts exposed to source cases was provided by health authorities.

Results:

There were 36 cases of healthcare acquired measles and 16 source cases (of which 14 could be identified). All source and secondary cases overlapped in time, and source cases, on average presented three times to a healthcare facility before being diagnosed. Eighty-four per cent of secondary cases acquired measles from a case with rash.

Conclusions:

The most recent measles outbreak in Australia has indicated that measles epidemiology post-elimination may differ to that during a period of measles control. Given that healthcare facilities are common settings for measles transmission in countries nearing or who already have reported elimination; understanding characteristics of healthcare setting transmissions can assist in effectively targeting prevention strategies.

Prologue

My role

Alexis and I were fortunate to commence the MAE during the year which would experience the biggest national measles outbreak in 15 years. Subsequently, we were part of the health department's surge staff, being on hand to assist at a local and state level. Our role started in April when we were introduced to contact tracing, interviewing individuals exposed to the index case of the outbreak. Following this we assisted in post-exposure prophylaxis clinics set up by Parramatta public health unit, this included weighing babies to ensure the appropriate volume of normal human immunoglobulin is received and also administration duties at the clinics. We also were mobilised to the Ministry of Health to conduct descriptive analysis on measles cases for the NSW Expert Working Group and also entered data for contact tracing lists. We also were mobilised to South West Sydney public health unit to enter data on cases into a new database they developed.

During the outbreak, a high proportion of cases were found to be acquired at a healthcare facility. As we were heavily involved in public health action from the beginning of the outbreak, Vicky suggested that we should be part of a team conducting analysis of healthcare acquired infections with the aim to submit a publication to a peer-reviewed journal. We would be responsible for drafting the paper which included conducting data analysis, interpreting the results and preparing the manuscript. Sophie Norton and Kirsty Hope were responsible for developing Table E-3 that is presented in this paper.

Lessons learned

This outbreak occurred one month after commencing the MAE program and it provided me with many lessons about working at a public health unit at a state and local level. Firstly, it was my first introduction into contact tracing. I was fortunate enough to have Vicky listen to my first interview. This was an extremely daunting experience however her feedback was invaluable. I learnt that I had to communicate succinctly and confidently and ensure that I provided correct information to individuals. I also learnt that it is important how one delivers a message, in some circumstances individuals may feel panic and anger at the potential of being exposed to an infectious individual.

During the post-exposure prophylaxis clinic, I learnt the algorithm for when the MMR vaccine is administered compared to the administration of NHIG. It was also clear that teamwork is imperative to the clinic running smoothly and ensuring everyone has clear roles and responsibilities allows greater efficiency.

I also was able to experience how it would be working at a local level and state level. It was interesting to see how they interacted together as well as the differences in priorities and public health action each had.

I learnt about the caveats of the data used for analysis. With the attack rate calculated, only healthcare contacts of index cases that transmitted infection at a healthcare setting were used as the denominator to calculate attack rates. This would have overestimated the overall attack rate for healthcare transmissions as there reports that 120 healthcare presentations of infectious cases of measles resulted in no transmissions. This calculation will be revised for the manuscript however at the time of writing my thesis; data of the number of contacts from these 120 healthcare presentations have not been extracted. Hence, the reasons that the attack rate was calculated as abovementioned.

In terms of the development of the manuscript, I learnt that it is important to choose what journal you want to submit the manuscript to before writing up, so you have an idea of the 'angle', structure and word count of the manuscript. It was also enlightening to collaborate with a number of public health units and try and overcome different expectations that each public health unit had for the evolution of the manuscript. During course block, Mahomed was instrumental in teaching us that messages that you want to communicate differ between a presentation and a manuscript. With much thought, we requested help from Mahomed into guiding us through the preparation of the manuscript. He taught me a great deal on how to write a manuscript and made me think outside the box on the key messages of the paper. This project allowed me to gain insight on how to write a paper and the important components of each section. He taught us that the strength of our study is determined by the validity of our data.

Public health action

This outbreak resulted in the exposure of numerous individuals to measles in a healthcare facility. The public health action was almost immediate following the confirmation of a measles case. Firstly, contact tracing occurred as soon as contact lists from medical centres and EDs were supplied. Individuals who were known to be infants < 12 months and pregnant were prioritised. Post-exposure prophylaxis clinics were organised at the paediatric hospital to administer MMR vaccine and NHIG if exposure occurred ≤ 5 days beforehand.

Our report highlighted the importance of healthcare transmission, particularly in an era of measles elimination. It describes the epidemiology of measles in this setting and has the potential to inform policy. This includes removing the 2-hour rule that is recommended in current guidelines for contact tracing in a healthcare facility, considering new approaches to raise awareness of measles among clinicians during periods of outbreaks and reconsidering when measles is most infectious.

We aim to submit the report below to the British Medical Journal as we believe that our observations are highly relevant for clinicians and public health staff in England and Wales. Our results provide lessons learned for Australia but also other countries striving for measles elimination and suggest that similar epidemiological observations will occur during periods of outbreaks once this has been achieved.

Acknowledgements

First and foremost, I would like to thank Vicky for providing us with so many opportunities to learn during this outbreak and advocating for our involvement throughout the outbreak. Also, to the public health nurses and public health registrar Shopna at the Parramatta public health unit who were so generous in advising us whenever we were unsure what to do. It was a wonderful experience to meet such passionate and encouraging individuals that made me feel like I was part of their team. I'd also like to thank Kirsty Hope and Sophie Norton from the South-Western Sydney public health unit who took a lot of their time out for this project and was always at hand to provide us with sound advice. Thank you to Alex Rosewell for mentoring Alexis and I during our time at the Ministry of Health. Lastly, to Mahomed I am most thankful that he was incredibly generous with his time in providing Alexis and I with so much guidance. Mahomed made me think about things I otherwise would not have thought of and inspired us to be better epidemiologists.

Please note that the results in the bound volume are still being reviewed by co-authors from the Ministry of NSW Health and are subject to revisions. The final manuscript for publication is yet to be approved by the NSW Ministry of Health.

Introduction

Between 2003 and 2008, Australia, England and Wales claimed to have eliminated the indigenous transmission of measles.^{6, 116} Despite this, all three countries have experienced a number of measles outbreaks in recent times.^{147, 148} This includes Wales' largest measles outbreak in 18 years, affecting 1325 individuals (at the time of writing).¹⁴⁹ For both England and Wales, a consequence of their large scale and persistent outbreaks has been the re-introduction of indigenous measles in 2008.¹⁵⁰ Australian outbreaks have comparably remained relatively small and it is likely that measles elimination has been sustained despite the largest outbreak in 15 years occurring in 2012. The United States (US) where measles elimination was declared in 2000,⁴⁵ has also witnessed recent outbreaks, with over 222 cases in 2011, the largest outbreak in the US since 2006.^{151, 152}

One key characteristic observed to have perpetuated the 2012 Australian outbreak was the numerous transmission which occurred in healthcare settings. Indeed, healthcare facilities have been reported as a prominent setting for measles transmissions in countries where measles is rare or eliminated.^{131, 153} Reasons for this are well documented, and include the low suspicion of infection among clinicians unfamiliar with the disease. This is further exacerbated by the difficulties inherent in diagnosing illness characterised by the non-differential symptoms shared by a myriad of other conditions.¹⁶ Additionally, measles is highly infectious and busy, highly dense environments like hospital EDs are optimal settings to propagate outbreaks.¹⁵³ Of concern is that the immunocompromised often frequent healthcare facilities, particularly hospitals and if infected, experience more severe disease outcomes than immunocompetent individuals.¹³¹

Contact tracing to identify susceptible individuals exposed to measles is often resource intensive.^{154, 155} Measles virus has been demonstrated to remain viable in air for up to two hours in a controlled experiment.¹⁵⁶ Previous published outbreaks have supported this finding, however are somewhat out-dated and occurred in an era where measles was still endemic.^{157, 158} These publications have dictated contact tracing guidelines in Australia which suggest all individuals present for up to two hours after a confirmed

measles case departs a healthcare facility should be contacted (referred to as the 'the two-hour rule').¹³⁴

Although numerous measles outbreak reports have been published describing healthcare transmissions,^{74, 106, 148} many reports often lack detailed case demographics and characteristics of transmissions are scarce. The 2012 outbreak in north-west England identified that nearly 30% of confirmed cases reported before March were exposed to a measles case in a healthcare setting.¹⁴⁸ A separate publication on this outbreak questioned why suspected cases were not isolated which resulted in 'a significant number' of secondary cases.¹⁵⁹ No further details were provided from these two reports. Similarly, little is known on the epidemiology of healthcare measles transmissions in Australia, particularly in the context of measles elimination. Because little has been published on the characteristics of healthcare transmissions during measles outbreaks, and because of the need for this type of evidence to inform prevention strategies and policies appropriate to a post-elimination setting, the objective of this study was to describe key characteristics of the 2012 NSW outbreak, focusing on healthcare acquired transmissions because of their prominent role fuelling outbreaks in countries where measles cases are rare. The three key characteristics described include: 1) The nature of exposure and exposure time between the source and secondary case; 2) The delay in diagnosis of measles in the source case and; 3) The stage of measles infection when transmission typically occurred.

Methods

Case series data describing confirmed measles cases were obtained from metropolitan Sydney Local Health Districts in Australia's most populous state, New South Wales, between April and November 2012. Western Sydney, where the majority of outbreak cases resided, is culturally diverse. A third of its two million population were born overseas and it also includes the largest urban population of Aboriginal and Torres Strait Islander people in the country.¹⁶⁰

A confirmed measles case required laboratory evidence or clinical signs of infection with an established epidemiological link.¹⁶¹ Clinicians and laboratories are legislatively required to notify public health authorities of suspected and confirmed measles cases.

¹⁶²

All confirmed cases temporally and regionally similar to the index case (i.e. the 25 year old Australian-born male who had returned to Australia from a trip to Thailand in April 2012) with genotype D8 or unknown were considered as belonging to this outbreak. Genotyping of specimens was conducted at the Victorian Infectious Diseases Reference Laboratory (VIDRL).

Health authorities interviewed cases using a standardised questionnaire to obtain demographic information (age, sex, ethnicity, and vaccination status), symptom onset date and movements during exposure and infectious periods. The exposure period was defined as seven to 18 days prior to rash onset whilst the infectious period was defined as five days prior to and four days after rash onset.

Electronic patient notes (including clinical history, movements in hospital, number of individuals exposed) were acquired from hospital ED files if cases had presented to an ED seven to 18 days preceding onset of symptoms during either the exposure or infectious period as defined above. For all ED cases, detail regarding arrival, triage, time seen and discharge times were available

A healthcare facility was defined as any premises that delivered healthcare services including hospital EDs, inpatient wards and GPs. A healthcare-acquired infection was a confirmed case between April and November 2012 who had a coincident attendance with a measles-infected individual at a healthcare facility seven to 18 days before symptom onset. These measles-infected individuals were defined as source cases of healthcare-acquired transmission.

Analysis was conducted using Stata^{®163} to describe demographic characteristics of source and secondary cases. Overlap times of source and secondary cases during presentation at a healthcare facility were calculated for each transmission event.

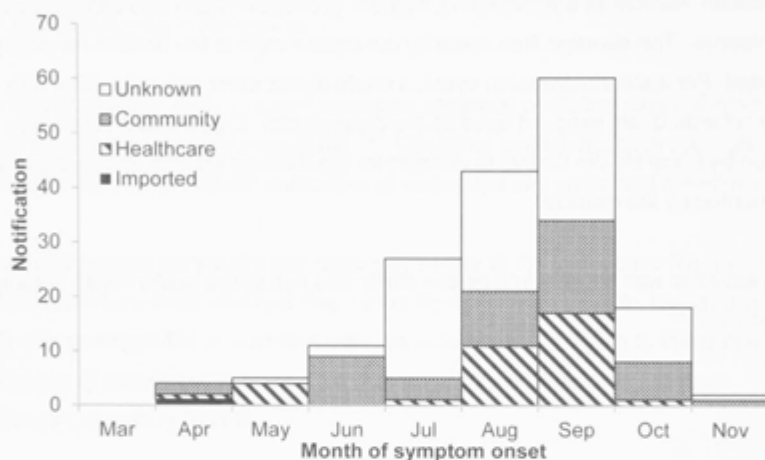
For source cases, proportions were calculated for type of healthcare facility of first presentation, number of presentations, number of cases isolated and symptoms during presentations. The average time spent by the source case in the healthcare facility was calculated. For each transmission event, a crude attack rates was calculated with number of individuals exposed used as the denominator. Crude attack rates were stratified by Local Health District to account for the different contact tracing procedures implemented by the districts.

Ethics approval was not required as this study was part of the public health response of the outbreak.

Results

There were 168 confirmed and 2 probable cases of measles, of which 36 (22%) were health-care acquired (Figure E-4).

Figure E-5. Confirmed and probable measles cases in the NSW outbreak by setting of transmission, April–November 2012



Healthcare acquired (secondary) cases

The median age of the healthcare-acquired cases was nine years (range: 5 months–37 years). Eleven cases (31%) were infants too young to be vaccinated, fourteen cases (39%), were unvaccinated and two cases (6%) received a dose of measles-mumps-rubella vaccine (MMR) following exposure as part of contact follow-up. One case (5%) had records of receiving two doses of MMR and three cases (8%) had received one dose of MMR. One case (5%) was a healthcare worker.

Thirty-three transmissions (33/36=92%) occurred in hospital, of which 29 transmissions (29/33=81%) occurred in an ED or ED waiting room and 4 transmissions (4/33=11%) in a ward. Three transmissions (3/36=8%) occurred at a GP.

Source cases

The median age of known source cases (n=14) was 16 years (range: 7 months–39 years). Two source cases acquired measles in a healthcare setting and were also included as a healthcare acquired case. Nine source cases (64%) were unimmunised and three source cases (21%) were too young to be immunised. One source case had documented evidence of a primary dose of MMR and the vaccination status of another source case was unknown. Two source cases could not be identified.

Overlap time between source and secondary case

The median overlap time between source and secondary cases was 4 hours and 24 minutes (range: 59 minutes–35 hours 31 minutes). All secondary cases were present at the same time of the source case and no transmissions occurred after the departure of the source case.

Of the known source cases that occurred in a GP clinic, presentation and departure times of patients were not recorded. However, one of the three secondary cases that were acquired in a GP reported that a measles case was known to be present during their attendance at the GP. For the 5 secondary cases that occurred in an ED where the source case remained unknown, 4 of the secondary cases overlapped with each other by time and place whilst the remaining secondary case overlapped in time with 3 possible source cases.

Delay in diagnosis

On average, source cases presented 3 times to a healthcare facility before being suspected of measles. The median number of days from symptom onset to notification was 5 (range:2–23) days and the median number of days from rash onset to notification was 2 (range:0–18) days. A total of 1251 contacts were subsequently exposed to measles from the 14 known source cases.

Of the 38 known healthcare presentations by a source case, isolation occurred upon initial presentation to an ED twice. Two other source cases were isolated after eight hours or more in the ED. A presentation of a source case to a GP resulted in isolation there; however, the source case re-presented at an ED on the same day and was not isolated. Three source cases were isolated upon admittance to a ward. Isolation patterns from the 14 known source cases did not appear to improve as the outbreak progressed (**Table E-3**).

Transmission characteristics

Of the known source cases, a total of 38 presentations to a healthcare facility occurred. Eighteen presentations occurred prior to rash onset and led to 5 transmissions (**Table E-3**). Twenty presentations occurred following rash onset and resulted in 25 transmissions. Sixteen per cent (n=6) of secondary cases acquired measles from a case without rash compared to 84% (n=30) of secondary cases who acquired measles from a case with rash.

In Western Sydney Local Health District, the crude attack rate for measles was 0.8% if the source case had no rash compared to 0.4% when the source case had a rash. In Sydney South West Local Health District, the crude attack rate for measles was 5.1% if the source case had no rash compared to 11.0% if the source case had a rash.

Table E-3. Healthcare presentation of source case by day of rash onset, NSW 2012

| Source case | Presentation day related to day of rash onset | | | | | | | | | | |
|---------------|---|--------------|-------------------------------|--------------|-------------|-------------------------|-----------------------------|--------------------------|--------------|--------------|--------------|
| | 5 days prior | 4 days prior | 3 days prior | 2 days prior | 1 day prior | Rash onset | 1 day post | 2 days post | 3 days post | 4 days post | >5 days post |
| 1 | | GP (NI) | | | GP (NI) | ED (NI) →1 D | | | | | |
| 2 ? ED →4 | | | | | | | | | | | |
| 3 | | | ED (NI) | | ED (NI) | ED (NI) →1 | Ward (NI) D | | | | |
| 4 | | | | | ED (NI) →3 | Ward (NI) | | | D | | |
| 5 | | | GP (NI) ED (NI) GP (NI) | | | ED (NI) →1 Ward (I) | D | | | | |
| 6 | | | | | | | GP (I) ED (NI) →1 | | | | D |
| 7 | | | | ED (NI) | | ED (NI) D | | | Ward (NI) →3 | Ward (NI) →1 | |
| 8 | | | | ? (I) | | ED (NI) →2 | Ward (I) D | | | | |
| 9 | | | | GP (NI) | | ED (NI) →1 D GP (NI) | | | | | |
| 10 | | | ED (NI) | GP (NI) | | ED (NI) →1 | | D | | | |
| 11 | | GP (NI) | | | | GP (NI) | | GP (NI) D ED (NI) →11 | | | |
| 12 | | | GP (NI) →1 | | | | D | | | | |
| 13 ? ED →1 | | | | | | | | | | | |
| 14 | | | | | | | →1 within this 5 day period | | | | |
| | | | | ED (NI) | Ward (NI) | Ward (NI) | Ward (NI) | Ward (NI) | Ward (NI) | | D |
| 15 GP (NI) →1 | | | | | | | | | | | |
| 16 | | | GP (NI) | | | | GP (NI) →1 ED (NI) | | | | D |

ED: Emergency Department; GP: General Practice; NI: Not isolated; I: Isolated; D: Diagnosis; →x: number of transmissions

Discussion

A key driver of the 2012 NSW measles outbreak was numerous healthcare setting transmissions, which occurred in part because of delayed diagnosis and implementation of control procedures. Key characteristics of healthcare acquired transmissions during the 2012 outbreak in NSW– the largest in Australia since 1997, have prompted health officials to reconsider public health response practices during measles outbreaks. Indeed, the results of this study suggest that a re-assessment of current knowledge in measles epidemiology is required, particularly in an era of measles elimination.

Contact tracing and the two-hour rule

The value of contact tracing individuals up to two hours after an infectious case has departed a healthcare facility is questionable. Australia's two-hour contact tracing rule appears to have been based on literature obtained during the 1960s to the 1980s. Under experimental conditions, measles virus was found to persist in air for up to 2 hours.¹⁵⁶ This was further supported by airborne transmission occurring up to two hours after an infectious case departed on a number of occasions,^{158, 164, 165} However, the number of transmissions from these reports was low (total of 6 secondary cases)^{158, 164-166} and all reports occurred in the United States at a time when measles was endemic, which would make identifying the source of infection challenging. Moreover, many of these reports described source cases who were vigorously coughing and likely to be 'superspreaders'.^{158, 164} Reviews on nosocomial measles transmissions continue to use these out-dated sources as evidence of virus persisting in air for up to two hours, even in updates^{131, 153}.

Among the known source cases in this study, no transmissions were observed to occur outside the direct time of exposure between the source case and susceptible individual in the healthcare setting. Although the overlap times between source and secondary case were missing for 8 transmissions, anecdotal evidence purports that an overlap time existed for one of these transmissions whilst another transmission had 3 possible source cases, all of whom overlapped in time with the secondary case. The overlap time for the remaining 6 transmissions cannot be precisely ascertained. Four of these were infected at the same time from an unknown source case. Though the source case remained unidentified, all secondary cases overlapped succinctly in time and place; however, we believe sufficient evidence still exists to question the necessity of 'the two-hour rule'. Hope et al 2013 also found all source and secondary cases to overlap in

time during a 2011 measles outbreak and concluded changes to the 'two-hour rule' may be warranted.¹³⁸ In England and Wales, only contacts with face-to-face exposure, exposure time excessive of 15 minutes or immunocompromised individuals with any contact (including over a short period after the measles case departed) are followed-up.¹³⁹

A potential limitation in this study, however was the differing contact tracing procedures that occurred in local health districts (LHD) in Sydney. One LHD contact traced according to the recommended 'two-hour rule' whilst another contact traced up to 15 minutes after the infectious case departed the healthcare facility. If a transmission had indeed occurred after 15 minutes, it would likely be captured by surveillance as measles is rare and Australia has a sensitive surveillance system. Furthermore, exposure at a healthcare facility would have been identified through case investigations.

To this point, it may be that the two-hour rule is unnecessary, moreover contributes to substantial proportion of costs of measles control efforts. An estimated USD 10 376 was spent in the US in 2008 for investigation and control efforts per measles case.¹⁶⁷ We suggest more targeted approach to contact tracing in Australia is adopted, particularly in the midst of an outbreak. Focusing only on individuals that are present at the same time as an infectious measles case in a healthcare setting would ideally minimise resource utilisation and be more appropriate for countries where measles is rare or eliminated.

Infectious stage of measles

It has long been recognised that infectiousness of measles is greatest during prodrome¹⁶⁸ whereas the appearance of a rash indicates the beginning of viral clearance from blood and tissue.¹⁶⁹ In this study however, a large proportion of healthcare transmission appeared to occur after the rash onset of the source case. Other reports have documented similar findings.^{47, 69} This may suggest that infectiousness could be just as high during the rash stage of illness as during the prodromal stage, through there are a number of caveats to this interpretation, including the small number of transmission events, variable wait times and times of exposure for the secondary cases. Additionally, there was one source case in this study that infected 11 secondary cases and this outlier may have skewed results. Nevertheless, attack rates were calculated by the number of individuals exposed at each presentation which may partially control for wait-times. It is unfortunate; however, that we were

unable to obtain information on the number of susceptible individuals at each presentation to obtain more valid attack rates.

Moreover, the attack rate may be an overestimate of the true attack rate. The denominator only included contacts of known source cases that transmitted in a healthcare setting. It excluded the healthcare contacts of index cases that were infectious whilst presenting to a healthcare facility that did not result in any known transmissions. During this outbreak, 120 (personal communication) presentations were reported to have occurred at a healthcare facility without any secondary transmission; however, at the time of writing, the number of contacts from these presentations was unknown.

Despite these limitations, the observation that, for this study, more secondary cases acquired measles from source cases that had rashes than source cases that were in the prodromal stage of infection may serve as a reminder of the importance of increasing suspicion when a patient presents with rash during times of outbreak. Additionally, infection can occur without presentation of a rash, particularly in the immunocompromised.¹⁴⁰ If this was to occur, it is likely more secondary cases would have resulted after a source case presented without rash, however, this was not observed.

One hypothesis to our results is that cough may be a stronger predictor of infectiousness than rash which is biologically plausible, given the route of transmission and documentation of index cases with rash and vigorous coughing resulting in a number of explosive outbreaks^{158, 164, 170}, however, more recent outbreak reports have limited information on cough severity. The frequency and rigour during this outbreak was not captured upon presentation in clinical notes during the 2012 outbreak and this kind of detail would have aided our understanding of transmission and it is therefore recommended that description of cough be better recorded in clinical notes.

Delayed diagnosis

Delayed diagnosis of measles cases was an ongoing issue during A recent review found that up to 50% of cases in developed countries, particularly where measles elimination was established had been acquired in a healthcare setting.¹⁷¹ On first presentation, only a low proportion of cases are suspected of having measles.¹¹⁹ Measles is difficult to clinically distinguish from other viral systemic illnesses. A patient in the early stages of measles may present with a combination of non-differential

symptoms including fever and perhaps only one of the following cough, coryza and conjunctivitis with differential diagnoses including influenza and other common respiratory viral infections and allergic rhinitis. Even with the characteristic maculopapular rash, a measles diagnosis may be overlooked because of the disease's rareness and similarities to adeno- and enteroviral infection, other exanths of childhood and drug allergy.^{47, 131} Lacking diagnosis, most cases presented multiple times to both the same healthcare facility of their first presentation and to other healthcare facilities. It is noteworthy to mention that although public health alerts were disseminated to healthcare facilities during this outbreak, including faxing and telephoning GPs in particularly affected areas, awareness did not appear heightened as multiple healthcare presentations by source cases were observed to occur even during the peak of the outbreak. More innovative approaches may be needed including alerts that are triggered when 'fever' and 'rash' are entered into electronic health records of primary health centres, however, such measures are yet to be evaluated.^{172, 173}

Our results identified that even during the peak of the outbreak, a number of measles cases were not suspected of having measles despite having a rash and subsequently were not isolated. Although a number of source cases were documented as being isolated, it was either too late as transmission had already occurred or isolation was ineffective. While isolation of an infectious case in a negative pressure room is the preferred method¹³⁴ in many situations this may not be feasible. More feasible options might include confinement of suspect cases in a single private room with a face mask¹⁷⁴, although busy EDs during winter, single rooms are scarce. Nevertheless, isolation practices were documented to have differed not only between hospitals but also within hospitals. Isolation practices could be more effective if procedures were more standardised and consistent.

Though several key limitation of this study have been detailed above, others are worth briefly noting. Though presentations by source cases to a healthcare facility may have been missed (presented at another GP/ ED) this is unlikely as cases were interviewed using a standardised questionnaire and are likely to recall seeking medical attention. There is a possibility that isolation of a suspected case could have occurred but was not captured in ED/GP medical records. If this was missing, the information would have been collected by public health authorities though communication with the clinician of a measles case. Ultimately, if time and resources permitted, it would have been ideal to compare the source cases who presented multiple times to a control group of individuals who were recognised immediately at a healthcare facility to determine if any

risk factors led to misdiagnosis of measles. New approaches are essential during periods of outbreaks to heighten awareness of disease among clinicians.

Conclusions

As more countries progress towards elimination, the predominant role of transmission in healthcare facilities must be noted. The most recent measles outbreak in Australia has indicated that measles epidemiology in an era of elimination may differ to that during a period of measles control. Contact tracing procedures based on out dated evidence may be revised to be more appropriate to the post-elimination context. Continual strengthening of the evidence base with outbreak reports such as this report will assist in improving the understanding of the pathogenicity of measles and consequently how best target awareness and education. Moreover improving clinician recognition and suspicion of measles – particularly during times of outbreak must continue to be prioritised with innovative strategies required. Without attempting to improve understanding of the current epidemiology of measles in an era of measles elimination may result in out dated and irrelevant measles control strategies. And the lack of relevant strategies may result in an increase in measles cases jeopardising the elimination status in Australia, and elsewhere.

References

1. Drutz JE. Measles: its history and its eventual eradication. *Seminars in Pediatric Infectious Diseases*. 2001;12(4):315-22.
2. Strebel PM, Cochi SL, Hoekstra E, Rota PA, Featherstone D, Bellini WJ, et al. A world without measles. *Journal of Infectious Diseases*. 2011;204(suppl 1):S1-S3.
3. Simons E, Ferrari M, Fricks J, Wannemuehler K, Anand A, Burton A, et al. Assessment of the 2010 global measles mortality reduction goal: results from a model of surveillance data. *The Lancet*. 2012;379(9832):2173-8.
4. World Health Organization. Global measles and rubella strategic plan: 2012-2020. Switzerland: 2012.
5. World Health Organization Regional Office for South-East Asia. Measles elimination by 2020. 2013 [cited 2013 27 Sept]; Available from: <http://www.searo.who.int/mediacentre/releases/2013/pr1565/en/index.html>.
6. Heywood A, Gidding HF, Riddell MA, McIntyre PB, MacIntyre CR, Kelly H. Elimination of endemic measles transmission in Australia. *Bull World Health Organ*. 2009;87:64-71.
7. Butel JS. Virology. Jawetz, Melnick, & Adelberg's medical microbiology. 25th ed. New York: McGraw-Hill Medical 2010.
8. Moss WJ, Griffin DE. Measles. *Lancet*. 2012;379:153-64.
9. Griffin DE, Ward BJ, Esolen LM. Pathogenesis of measles virus infection: an hypothesis for altered immune responses. *Journal of Infectious Diseases*. 1994;170(Supplement 1):S24-S31.
10. Perry RT, Halsey NA. The clinical significance of measles: a review. *Journal of Infectious Diseases*. 2004;189(Supplement 1):S4-S16.
11. Centers for Disease Control and Prevention. Measles. In: Atkinson W, Wolfe S, Hamborsky J, editors. *Epidemiology and Prevention of Vaccine-Preventable Diseases*. 12th ed. ed. Washington: Public Health Foundation; 2012. p. 173-92.
12. Heymann DL. *Control of communicable diseases manual*: American Public Health Association; 2008.
13. Fitzgerald TL, Durrheim DN, Merritt TD, Birch C, Tran T. Measles with a possible 23 day incubation period. *Commun Dis Intell*. 2012;36(3):E277-E80.
14. Ferson MJ, Young LC, Robertson PW, Whybin LR. Difficulties in clinical diagnosis of measles: proposal for modified clinical case definition. *The Medical journal of Australia*. 1995;163(7):364.
15. Lambert SB, Kelly HA, Andrews RM, Catton MC, Lynch PA, Leydon JA, et al. Enhanced measles surveillance during an interepidemic period in Victoria. *Medical Journal of Australia*. 2000;172(3):114-8.
16. Durrheim DN, Kelly H, Ferson MJ, Featherstone D. Remaining measles challenges in Australia. *Medical Journal of Australia*. 2007;187(3):181-4.
17. Strebel PM, Papania MJ, Fiebelkorn AP, Halsey NA. Measles vaccine. In: Plotkin SA, Orenstein WA, Offit PA, editors. *Vaccines*. 6th ed. Philadelphia: Elsevier Saunders; 2013. p. 352-87.
18. Centers for Disease Control and Prevention. *Epidemiology and Prevention of Vaccine-Preventable Diseases*. 12th ed. Washington DC: Public Health Foundation; 2012.
19. Communicable Diseases Network of Australia. *Measles: National Guidelines for Public Health Units*. 2009.
20. World Health Organization. *Manual for the laboratory diagnosis of measles and rubella virus infection*. Geneva, Switzerland: World Health Organization, 2007.
21. Public Health Laboratory Network. *Measles Laboratory Case Definition*. Canberra 2009 [updated 6 August 2010; cited 2013 28 June]; Available from: <http://www.health.gov.au/internet/main/publishing.nsf/Content/cda-phlncd-measles.htm>.

22. National Health and Medical Research Council. The Australian immunisation handbook. 10th edition. Canberra 2013.
23. National Health and Medical Research Council. The Australian immunisation handbook. 9th edition. Canberra 2008.
24. McLean HQ, Fiebelkorn AP, Temte JL, Wallace GS. Prevention of Measles, Rubella, Congenital Rubella Syndrome, and Mumps, 2013: Summary Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR - Morbidity & Mortality Weekly Report*. 2013;62(RR04):1-34.
25. Leuridan E, Van Damme P. Passive transmission and persistence of naturally acquired or vaccine-induced maternal antibodies against measles in newborns. [Review] [65 refs]. *Vaccine*. 2007;25(34):6296-304.
26. Leuridan E, Hens N, Hutse V, Ieven M, Aerts M, Van Damme P. Early waning of maternal measles antibodies in era of measles elimination: longitudinal study. *BMJ*. 2010;340.
27. Gans HA, Arvin AM, Galinus J, Logan L, DeHovitz R, Maldonado Y. Deficiency of the humoral immune response to measles vaccine in infants immunized at age 6 months. *Jama-Journal of the American Medical Association*. 1998;280(6):527-32.
28. Gans H, Yasukawa L, Rinki M, DeHovitz R, Forghani B, Beeler J, et al. Immune responses to measles and mumps vaccination of infants at 6, 9, and 12 months. *Journal of Infectious Diseases*. 2001;184(7):817-26.
29. Uzicanin A, Zimmerman L. Field effectiveness of live attenuated measles-containing vaccines: a review of published literature. *Journal of Infectious Diseases*. 2011;204(suppl 1):S133-S49.
30. Demicheli V, Rivetti A, Debalini MG, Di Pietrantonj C. Vaccines for measles, mumps and rubella in children. *Cochrane Database Syst Rev*. 2012;2.
31. De Serres G, Boulianne N, Defay F, Brousseau N, Benoît M, Lacoursière S, et al. Higher risk of measles when the first dose of a 2-dose schedule of measles vaccine is given at 12–14 months versus 15 months of age. *Clinical infectious diseases*. 2012;55(3):394-402.
32. Retief F, Cilliers L. Measles in antiquity and the Middle Ages. *South African Medical Journal*. 2010;100(4):216-7.
33. Ligon BL. Biography: Rhazes: His career and his writings. *Seminars in Pediatric Infectious Diseases*. 2001;12(3):266-72.
34. Paterson BJ, Kirk MD, Cameron AS, D'Este C, Durrheim DN. Historical data and modern methods reveal insights in measles epidemiology: a retrospective closed cohort study. *BMJ Open*. 2013;3(e002033).
35. Cumpston JHL. The history of diphtheria, scarlet fever, measles, and whooping cough in Australia. 37. SpN, editor. Canberra: Commonwealth of Australia, Department of Health; 1927.
36. Edmunds WJ, Gay NJ, Kretzschmar M, Pebody R, Wachmann H. The pre-vaccination epidemiology of measles, mumps and rubella in Europe: implications for modelling studies. *Epidemiology and infection*. 2000;125(3):635-50.
37. Hall R. Notifiable Diseases Surveillance, 1917 to 1991. *Commun Dis Intell*. 1993;17(11):226-36.
38. Gidding HF, Burgess MA, Kempe AE. A short history of vaccination in Australia. *Medical Journal of Australia*. 2001;174(1):37-40.
39. National Centre for Immunisations Research and Surveillance. NCIRS vaccination history tables. Sydney 2012 [updated 31 July 2012; cited 2012 25 October]; Available from: <http://www.ncirs.edu.au/immunisation/history/index.php>.
40. Hargreaves J, Longbottom H, Myint H, Herceg A, Oliver G, Curran M, et al. Annual report of the National Notifiable Diseases Surveillance System, 1994. *Communicable Diseases Intelligence*. 1995;19:542-74.
41. Sencer DJ, Dull HB, Langmuir AD. Epidemiologic basis for eradication of measles in 1967. *Public health reports*. 1967;82(3):253.

42. Henao-Restrepo A-M, Strebel P, Hoekstra EJ, Birmingham M, Bilous J. Experience in global measles control, 1990–2001. *Journal of Infectious Diseases*. 2003;187(Supplement 1):S15–S21.
43. World Health Organization. Measles: Progress towards global control and regional elimination 1998–1999. *Wkly Epidemiol Rec*. 1999;74(50):429–34.
44. Organization WH. Strategies for reducing global measles mortality. *Wkly Epidemiol Rec*. 2000;75:409–16.
45. Katz SL, Hinman AR. Summary and conclusions: measles elimination meeting, 16–17 March 2000. *Journal of Infectious Diseases*. 2004;189(Supplement 1):S43–S7.
46. Perry RT, Gacic-Dobo M, Dabbagh A, Strebe PM, Okwo-Bele J-M, Goodson JL. Global Control and Regional Elimination of Measles, 2000–2011. *Morbidity and Mortality Weekly Report*. 2013;62(2):27–31.
47. WHO Regional Committee for the Western Pacific. Measles elimination, hepatitis B control and poliomyelitis eradication. Report of the regional committee summary records of the plenary meetings. Manila, 2005. p. 214–5.
48. Progress Toward Measles Elimination — Western Pacific Region, 2009–2012. *Morbidity and Mortality Weekly Report*. 2013;62(22):443–7.
49. World Health Organization. Proceedings of the Global Technical Consultation to Assess the Feasibility of Measles Eradication, 28–30 July 2010. *Journal of Infectious Diseases*. 2011;204(Suppl 1):S4–S13.
50. Decade of Vaccine Collaboration. Global Vaccine Action Plan. *Vaccine*. 2013;31S:B5–B31.
51. World Health Organization. Framework for verifying elimination of measles and rubella. *Weekly Epidemiological Record*. 2013;9(88):89–100.
52. McIntyre P, Amin J, Gidding H, Hull B, Torvaldsen S, Tucker A, et al. Vaccine preventable diseases and vaccination coverage in Australia, 1993–1998. *Communicable Diseases Intelligence*. June 2000((Supplement)).
53. McDonnell LF, Jorm LR. Measles epidemic in western Sydney. *New South Wales Public Health Bulletin*. 1994;5(6):59–60.
54. Patel M, Lush D. Measles vaccine effectiveness in central Australian aboriginal children vaccinated at or after eight months of age. *Australian & New Zealand Journal of Public Health*. 1998;22(6):729–30.
55. Jeremijenko A, Kelly H, Patel M. The high morbidity associated with a measles outbreak in a West Australian town. *Journal of Paediatrics and Child Health*. 1996;32(5):382–5.
56. Herceg A, Oliver G, Myint H, Andrews G, Curran M, Crerar S, et al. Annual Report of the National Notifiable Diseases Surveillance System, 1995. *Communicable Diseases Intelligence*. 1996;20:440–64.
57. Curran M, Harvey B, Crerar S, Oliver G, D'Souza R, Htoo Myint CR, et al. Australia's notifiable diseases status, 1996. *Commun Dis Intell*. 1997;21:281–307.
58. Campbell M. Young adult measles vaccination. *Communicable Diseases Intelligence*. 2000;24:241–2.
59. Turnbull FM, Burgess MA, McIntyre PB, Lambert SB, Gilbert GL, Gidding HF, et al. The Australian measles control campaign, 1998. *Bull World Health Organ*. 2001;79(9):882–8.
60. Roche P, Spencer J, Lin M, Gidding H, Kirk M, Eyeson-Annan M, et al. Australia's notifiable diseases status, 1999. Annual report of the National Notifiable Diseases Surveillance System *Commun Dis Intell*. 2001;25:190–245.
61. Lambert SB, Morgan ML, Riddell MA, Andrews RM, Kelly HA, Leydon JA, et al. Measles outbreak in young adults in Victoria, 1999. *The Medical journal of Australia*. 2000;173(9):467.
62. Gilbert GL, Escott RG, Gidding HF, Turnbull FM, Heath TC, McIntyre PB, et al. Impact of the Australian Measles Control Campaign on immunity to measles and rubella. *Epidemiology & Infection*. 2001;127(2):297–303.

63. MacIntyre C, Gay N, Gidding H, Hull B, Gilbert G, McIntyre P. A mathematical model to measure the impact of the Measles Control Campaign on the potential for measles transmission in Australia. *International journal of infectious diseases*. 2002;6(4):277-82.
64. Chibo D, Birch CJ, Rota PA, Catton MG. Molecular characterization of measles viruses isolated in Victoria, Australia, between 1973 and 1998. *Journal of General Virology*. 2000;81(10):2511.
65. Chibo D, Riddell M, Catton M, Birch C. Novel measles virus genotype, East Timor and Australia. *Emerging Infectious Diseases*. 2002;8(7):735-7.
66. Lin M, Roche P, Spencer J, Milton A, Wright P, Witteveen D, et al. Australia's notifiable diseases status, 2000. *Commun Dis Intell*. 2002;26(2):118-203.
67. Holland R, Hall R. A cluster of measles. *Communicable Diseases Intelligence*. 2000;24(5):142-3.
68. Hanna J, Richards A, Young D, Hills S, Humphreys J. Measles in health care facilities: some salutary lessons. *Communicable Diseases Intelligence*. 2000;24(7):211-2.
69. Outbreak report: measles cluster in south-eastern Sydney with transmission in a general practice waiting room. *Commun Dis Intell*. 2001;25(1).
70. Brotherton J, McIntyre P, Puech M, Wang H, Gidding H, Hull B, et al. Vaccine preventable diseases and vaccination coverage in Australia, 2001 to 2002. *Commun Dis Intell*. 2004;28(Suppl 2):S41-S5.
71. Davidson N, Andrews R, Riddell M, Leydon J, Lynch P. A measles outbreak among young adults in Victoria, February 2001. *Communicable Diseases Intelligence*. 2002;26(2):273-8.
72. Gidding H, Gilbert G. Measles immunity in young Australian adults. *Communicable Diseases Intelligence*. 2001;25(3):133-6.
73. Kelly HA, Gidding HF, Karapanagiotidis T, Leydon JA, Riddell MA. Residual susceptibility to measles among young adults in Victoria, Australia following a national targeted measles-mumps-rubella vaccination campaign. *BMC Public Health*. 2007;7(99).
74. Chapman S, MacKenzie R. Fainting schoolgirls wipe \$ A1bn off market value of Gardasil producer. *BMJ*. 2007;334(7605):1195-.
75. Weston KM, Dwyer DE, Ratnamohan M, McPhie K, Chan S-w, Branley JM, et al. Nosocomial and community transmission of measles virus genotype D8 imported by a returning traveller from Nepal. *Commun Dis Intell Q Rep*. 2003;30(3):358-65.
76. Yohannes K, Roche P, Roberts A, Liu C, Firestone S, Bartlett M, et al. Australia's notifiable diseases status, 2004, annual report of the National Notifiable Diseases Surveillance System. *Communicable Diseases Intelligence*. 2006;30(1):1.
77. Owen R, Roche PW, Hope K, Yohannes K, Roberts A, Liu C, et al. Australia's notifiable diseases status, 2005: annual report of the National Notifiable Diseases Surveillance System. *Communicable Diseases Intelligence*. 2007;31(1):1.
78. Begg K, Roche P, Owen R, Liu C, Kaczmarek M, Hii A, et al. Australia's notifiable disease status, 2006: annual report of the National Notifiable Diseases Surveillance System. *Communicable Diseases Intelligence*. 2008;32(2):89-154.
79. Martin N, Foxwell AR. Measles status in Australia, and outbreaks in the first quarter of 2009. *Communicable Diseases Intelligence*. 2009;33(2):225-31.
80. NNDSS Annual Report Writing Group. Australia's Notifiable Disease Status, 2009: Annual Report of the National Notifiable Disease Surveillance System. *Commun Dis Intell*. 2011;35(2):61-131.
81. McIntyre P, Gidding H, Gilmour R, Lawrence G, Hull B, Horby P, et al. Vaccine preventable diseases and vaccination coverage in Australia, 1999 to 2000. *Communicable Diseases Intelligence*. 2002;26(Suppl):1-111.
82. Chibo D, Riddell M, Catton M, Lyon M, Lum G, Birch C. Studies of measles viruses circulating in Australia between 1999 and 2001 reveals a new genotype. *Virus Research*. 2003;91(2):213-21.

83. Brotherton J, Wang H, Schaffer A, Quinn H, Menzies R, Hull B, et al. Vaccine preventable diseases and vaccination coverage in Australia, 2003 to 2005. *Communicable Diseases Intelligence*. 2007;31:S1.
84. Huppatz C, Durrheim DN, Levi C, Dalton C, Williams D, Clements MS, et al. Etiology of encephalitis in Australia, 1990–2007. *Emerging Infectious Diseases*. 2009;15(9):1359.
85. Chiu C, Dey A, Wang H, Menzies R, Deeks S, Mahajan D, et al. Vaccine preventable diseases in Australia, 2005 to 2007. *Communicable Diseases Intelligence*. 2010;34 Suppl:ix-S167.
86. Ministry of Health New South Wales (NSW). Occupational Assessment, Screening and Vaccination Against Specified Infectious Diseases. 2011 [cited 2013 3 October]; PD2011_005]. Available from: http://www0.health.nsw.gov.au/policies/pd/2011/pdf/PD2011_005.pdf.
87. National Health and Medical Research Council. Australian Guidelines for the Prevention and Control of Infection in Healthcare.. Canberra: Australian Government, 2010.
88. Hull B, Deeks S, Menzies R, McIntyre P. Immunisation coverage annual report, 2007. *Commun Dis Intell*. 2009;33(2):170-87.
89. Field guidelines for measles elimination. World Health Organization Regional Office for the Western Pacific, 2004.
90. Hull BP, Mahajan D, Dey A, Menzies RI, McIntyre PB. Immunisation coverage annual report, 2008. *Commun Dis Intell*. 2010;34(3):241-58.
91. Beard FH, Franklin LJ, Donohue SD, Moran RJ, Lambert SB, Maloney ME, et al. Contact tracing of in-flight measles exposures: lessons from an outbreak investigation and case series, Australia, 2010. *Western Pacific Surveillance and Response Journal*. 2011;2(3):1-9.
92. Queensland Health. Vaccination of Health Care Workers. 2012 [cited 2013 3 October]; Available from: <http://www.health.qld.gov.au/ghpolicy/docs/qdl/gh-qdl-321-9.pdf>.
93. Fabian VA, Lee H-Y, Keith-Rokosh JL, de Souza J-L, Stewart-Wynne E. A 22-year-old Australian woman with atypical subacute sclerosing panencephalitis diagnosed at postmortem. *Journal of Clinical Neuroscience*. 2010;17(9):1192-4.
94. Centers for Disease Control and Prevention. Notes from the field: Multiple cases of measles after exposure during air travel--Australia and New Zealand, January 2011. *MMWR - Morbidity & Mortality Weekly Report*. 2011;60(25):851.
95. Coleman KP, Markey PG. Measles transmission in immunized and partially immunized air travellers. *Epidemiology & Infection*. 2010;138(7):1012-5.
96. Flego K, Sheppard V, McPhie K. A recent measles outbreak in Western Sydney- diagnosis and population vaccination status. *The Broad Street Pump-Centre for Infectious Diseases and Microbiology Public Health*. 2011(23).
97. NNDSS Annual Report Writing Group. Australia's Notifiable Disease Status, 2009: Annual Report of the National Notifiable Diseases Surveillance System. *Communicable Diseases Intelligence*. 2011;35(2):61-131.
98. Department of Health and Ageing. Australian national notifiable diseases case definitions: Measles case definition. [updated 12 March, 2004; cited 2012 17 August]; Available from: http://www.health.gov.au/internet/main/publishing.nsf/Content/cda-surveil-nndss-casedefs-cd_meas1.htm.
99. Communicable Diseases Network Australia. National Notifiable Diseases Surveillance System.
100. Australian Bureau of Statistics. Underlying cause of death, All causes, Australia. 2002–2011.
101. Cáceres VM, Strebel PM, Sutter RW. Factors determining prevalence of maternal antibody to measles virus throughout infancy: a review. *Clinical infectious diseases*. 2000;31(1):110.

102. Freedman DO, Weld LH, Kozarsky PE, Fisk T, Robins R, von Sonnenburg F, et al. Spectrum of disease and relation to place of exposure among ill returned travelers. *New England Journal of Medicine*. 2006;354(2):119-30.
103. O'Brien DP, Leder K, Matchett E, Brown GV, Torresi J. Illness in Returned Travelers and Immigrants/Refugees: The 6-Year Experience of Two Australian Infectious Diseases Units. *Journal of travel medicine*. 2006;13(3):145-52.
104. MacIntyre CR, Ackland MJ, Chandraraj EJ, Pilla JE. Accuracy of ICD-9-CM codes in hospital morbidity data, Victoria: implications for public health research. *Australian and New Zealand Journal of Public Health*. 1997;21(5):477-82.
105. World Health Organization. Global eradication of measles: report by the Secretariat. Geneva, Switzerland: Sixty-third World Health Assembly., 2010.
106. Sniadack DH, Mendoza-Aldana J, Jee Y, Bayutas B, Lorenzo-Mariano KM. Progress and challenges for measles elimination by 2012 in the Western Pacific Region. *Journal of Infectious Diseases*. 2011;204(suppl 1):S439-S46.
107. National Centre for Immunisation Research and Surveillance of Vaccine Preventable Diseases. *Vaccine Preventable Diseases in Australia, 2005-2007*. Communicable Diseases Intelligence. 2010;34 Supplement.
108. Gidding H. The impact of Australia's measles control programme over the past decade. *Epidemiology and infection*. 2005;133(01):99-105.
109. De Serres G, Gay NJ, Farrington CP. Epidemiology of transmissible diseases after elimination. *American Journal of Epidemiology*. 2000;151(11):1039-48.
110. Fraser C. Estimating individual and household reproduction numbers in an emerging epidemic. *PLoS One*. 2007;2(8):e758.
111. Gao Z, Wood JG, Burgess MA, Menzies RI, McIntyre PB, MacIntyre CR. Models of strategies for control of rubella and congenital rubella syndrome—A 40 year experience from Australia. *Vaccine*. 2013;31(4):691-7.
112. Gidding H. Australia's national serosurveillance program. *New South Wales Public Health Bulletin*. 2003;14(5):90-3.
113. Jardine A, Deeks SL, Patel MS, Menzies RI, Gilbert GL, McIntyre PB. An evaluation of the Australian National Serosurveillance Program. *Commun Dis Intell*. 2010;34:29-36.
114. Gay NJ, De Serres G, Farrington PC, Redd SB, Papania MJ. Assessment of the status of measles elimination from reported outbreaks: United States, 1997–1999. *Journal of Infectious Diseases*. 2004;189(Supplement 1):S36-S42.
115. King A, Varughese P, De Serres G, Tipples G, Waters J. Measles elimination in Canada. *Journal of Infectious Diseases*. 2004;189(Supplement 1):S236-S42.
116. Ramsay ME, Jin L, White J, Litton P, Cohen B, Brown D. The elimination of indigenous measles transmission in England and Wales. *Journal of Infectious Diseases*. 2003;187(Supplement 1):S198-S207.
117. Becker NG, Li Z, Hsu E, Andrews RM, Lambert SB. Monitoring measles elimination in Victoria. *Australian and New Zealand Journal of Public Health*. 2007;29(1):58-63.
118. Department of Health and Ageing. *NNDSS Core Dataset: Dataset Field Specifications--version 9.3*. Canberra 2009.
119. Farrington CP, Grant AD. The distribution of time to extinction in subcritical branching processes: Applications to outbreaks of infectious disease. *Journal of Applied Probability*. 1999;36(3):771-9.
120. StataCorp. 2011. *Stata Statistical Software: Release 12*. College Station TSL.
121. MATLAB version 7.10.0 Natick, Massachusetts: The MathWorks Inc.; 2010.
122. Gidding HF, Wood J, MacIntyre CR, Kelly H, Lambert SB, Gilbert GL, et al. Sustained measles elimination in Australia and priorities for long term maintenance. *Vaccine*. 2007;25(18):3574-80.
123. Hull B, Dey A, Mahajan D, Menzies R, McIntyre PB. Immunisation coverage annual report, 2009. *Communicable Diseases Intelligence*. 35(2):132-48.

124. Harpaz R, Papania MJ, McCauley MM, Redd SB. Has surveillance been adequate to detect endemic measles in the United States? *Journal of Infectious Diseases*. 2004;189(Supplement 1):S191-S5.
125. Machaira M, Papaevangelou V. Current Measles Outbreaks: Can We Do Better for Infants at Risk? *The Pediatric Infectious Disease Journal*. 2012;31(7):756-8.
126. Orenstein WA, Harpaz R, Papania MJ. Can a minimum rate of investigation of measleslike illnesses serve as a standard for evaluating measles surveillance? *Journal of Infectious Diseases*. 2004;189(Supplement 1):S204-S9.
127. Wang Y, Andrews R, Kelly H, Lambert S. Evaluating measles surveillance using laboratory-discarded notifications of measles-like illness during elimination. *Epidemiology and infection*. 2007;135(8):1363-8.
128. Institute for Clinical Pathology and Medical Research. [updated 9 November 2009; cited 2013 12 October]; Available from: <http://sydney.edu.au/medicine/westmead/research/icpmr.php>.
129. South Eastern Area Laboratory Services. 2011 [cited 2013 12 October]; Available from: <http://www.seals.health.nsw.gov.au/about-us/.aspx>.
130. Hunter Area Pathology Service. 2011 [cited 2013 12 October]; Available from: <http://haps.nsw.gov.au/page18666/About-Us.aspx>.
131. Botelho-Nevers E, Gautret P, Biellik R, Brouqui P. Nosocomial transmission of measles: An updated review. *Vaccine*. 2012;30(27):3996-4001.
132. Durrheim DN, Speare R, Ogunbanjo GA. Elimination programs: Monitoring the effectiveness of surveillance. *Journal of Infectious Diseases*. 2004;190(12):2195-6.
133. Harpaz R, Papania MJ. Elimination programs: Monitoring the effectiveness of surveillance - Reply. *Journal of Infectious Diseases*. 2004;190(12):2196-7.
134. Australian Government Department of Health and Ageing. Series of national guidelines. Measles. National guidelines for public health units. . 2009 [updated 19 February 2009; cited 2012 21 November]; Available from: <http://www.health.gov.au/internet/main/publishing.nsf/Content/cdna-song-measles.htm>.
135. Bozzola E, Quondamcarlo A, Krzysztofak A, Lancella L, Romano M, Tozzi A. Re-emergence of measles in young infants. *Pediatric Infectious Disease Journal*. 30(3):271.
136. Klinge J, Lugauer S, Korn K, Heininger U, Stehr K. Comparison of immunogenicity and reactogenicity of a measles, mumps and rubella (MMR) vaccine in German children vaccinated at 9-11, 12-14 or 15-17 months of age. *Vaccine*. 2000;18(27):3134-40.
137. De Serres G, Boulianne N, Defay F, Brousseau N, Benoit M, Lacoursiere S, et al. Higher risk of measles when the first dose of a 2-dose schedule of measles vaccine is given at 12-14 months versus 15 months of age. *Clinical Infectious Diseases*. 2012;55(3):394-402.
138. Hope K, Boyd R, Conaty S, Maywood P. Measles transmission in health care waiting rooms: implications for public health response. *Western Pacific Surveillance and Response*. 2012;3(4).
139. Health Protection Agency. HPA National Measles Guidelines-Local & Regional Services. 2010.
140. Orenstein WA, Perry RT, Halsey NA. The clinical significance of measles: a review. *Journal of Infectious Diseases*. 2004;189(Supplement 1):S4-S16.
141. Coleman K, Markey P. Measles transmission in immunized and partially immunized air travellers. *Epidemiology and infection*. 2010;138(07):1012-5.
142. Department of Health and Ageing. National Immunisation Program Schedule. 2012 [updated 15 June, 2012 cited 2012 20 July]; Available from: <http://immunise.health.gov.au/internet/immunise/publishing.nsf/Content/nips2>.
143. Bowen AC, Ferson MJ, Palasanthiran P. Consequences of an unrecognized measles exposure in an emergency department. *Emergency Medicine Australasia*. 2009;21(6):491-6.

144. Chen SY, Anderson S, Kutty PK, Lugo F, McDonald M, Rota PA, et al. Health Care-Associated Measles Outbreak in the United States After an Importation: Challenges and Economic Impact. *Journal of Infectious Diseases*. 2011;203(11):1517-25.
145. Choi WS, Sniadack DH, Jee Y, Go UY, So JS, Cho H, et al. Outbreak of measles in the Republic of Korea, 2007: Importance of nosocomial transmission. *Journal of Infectious Diseases*. 2011;204(suppl 1):S483-S90.
146. Groth C, Bottiger B, Plesner A, Christiansen A, Glismann S, Hogh B. Nosocomial measles cluster in Denmark following an imported case, December 2008-January 2009. *Euro surveillance*. 2009;14(8).
147. Wise J. Measles outbreak hits northeast England. *BMJ*. 2013;346(f662).
148. Vivancos R, Keenan A, Farmer S, Atkinson J, Coffey E, Dardamassis E, et al. An ongoing large outbreak of measles in Merseyside, England, January to June 2012. *Euro surveillance*. 2012;17(29).
149. Public Health Wales. Measles outbreak cases rise again as school vaccinations enter final week. 2013 [updated 21 May 2013; cited 2013 29 May]; Available from: <http://www.wales.nhs.uk/sitesplus/888/news/27327>.
150. Measles once again endemic in the United Kingdom. *Euro Surveillance: Bulletin European sur les Maladies Transmissibles = European Communicable Disease Bulletin*. 2008;13(27):3.
151. Parker AA, Staggs W, Dayan GH, Ortega-Sánchez IR, Rota PA, Lowe L, et al. Implications of a 2005 measles outbreak in Indiana for sustained elimination of measles in the United States. *New England Journal of Medicine*. 2006;355(5):447-55.
152. Centers for Disease Control and Prevention (CDC). Measles — United States, 2011. Morbidity and mortality weekly report. 2012;61(253-257).
153. Biellik R, Clements CJ. Strategies for minimizing nosocomial measles transmission. *Bulletin of the World Health Organization*. 1997;75(4):367.
154. Stuart RL, Bradford J, Leszkiewicz P, Wilson J, Gillespie EE. The costs of containing measles within a health care service. *Healthcare Infection*. 2010;15(2):43-6.
155. Coleman MS, Garbat-Welch L, Burke H, Weinberg M, Humbaugh K, Tindall A, et al. Direct costs of a single case of refugee-imported measles in Kentucky. *Vaccine*. 2012;30(2):317-21.
156. De Jong J, Winkler K. Survival of measles virus in air. *Nature*. 1964;201:1054-5.
157. Remington PL, Hall WN, Davis IH, Herald A, Gunn RA. Airborne transmission of measles in a physician's office. *JAMA: the journal of the American Medical Association*. 1985;253(11):1574-7.
158. McIntyre PB, Gidding HF, Gilbert GL. Measles in an era of measles control [editorial]. *Medical Journal of Australia*. 2000;172(3):103-4.
159. Lamden KH, Vivancos R, McCann R, Ghebrehewet S. Why is measles so difficult? *BMJ*. 2013;346(f245).
160. NSW Government. About Western Sydney--Demographics [cited 2013 30 May]; Available from: <http://www.westernsydney.nsw.gov.au/about-western-sydney/demographics/>.
161. Department of Health and Ageing. Australian national notifiable diseases case definitions- Measles case definition. 2004 [updated 12 March, 2004; cited 2012 21 November]; Available from: http://www.health.gov.au/internet/main/publishing.nsf/Content/cda-surveil-nndss-casedefs-cd_meas1.htm.
162. New South Wales Government. Public Health Act 2010 No 127. [cited 2012 November 23]; online:[Available from: <http://www.legislation.nsw.gov.au/viewtop/inforce/act+10+1991+FIRST+0+N/>].
163. StataCorp. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP; 2011.
164. Remington PL, Hall WN, Davis IH, Herald A, Gunn RA. Airborne transmission of measles in a physician's office. *JAMA*. 1985;253(11):1574-7.

165. Sienko DG, Friedman C, McGee H, Allen M, Simonsen WF, Wentworth BB, et al. A measles outbreak at university medical settings involving health care providers. *American Journal of Public Health*. 1987;77(9):1222-4.
166. Measles--Hawaii. Morbidity and mortality weekly report. 1984;33(50):702, 7-11.
167. Sugerman DE, Barskey AE, Delea MG, Ortega-Sanchez IR, Bi D, Ralston KJ, et al. Measles outbreak in a highly vaccinated population, San Diego, 2008: role of the intentionally undervaccinated. *Pediatrics*. 2010;125(4):747-55.
168. Perry RT, Halsey NA. The clinical significance of measles: A review. *Journal of Infectious Diseases*. 2004;189:S4-S16.
169. Griffin DE, Ward BJ, Esolen LM. Pathogenesis of measles-virus infections- an hypothesis for altered immune-responses. *Journal of Infectious Diseases*. 1994;170:S24-S31.
170. Chen RT, Goldbaum GM, Wassilak SG, Markowitz LE, Orenstein WA. An explosive point-source measles outbreak in a highly vaccinated population modes of transmission and risk factors for disease. *American Journal of Epidemiology*. 1989;129(1):173-82.
171. Maltezou HC, Wicker S. Measles in health-care settings. *American Journal of Infection Control*. 2013.
172. Lurio J, Morrison FP, Pichardo M, Berg R, Buck MD, Wu W, et al. Using electronic health record alerts to provide public health situational awareness to clinicians. *Journal of the American Medical Informatics Association*. 2010;17(2):217-9.
173. Revere D, Nelson K, Thiede H, Duchin J, Stergachis A, Baseman J. Public health emergency preparedness and response communications with health care providers: A literature review. *BMC public health*. 2011;11(1):337.
174. Seigel J, Rhinehart E, Jackson M, Chiarello L. 2007 guideline for isolation precautions: preventing transmission of infectious agents in health care settings. *American Journal of Infection Control*. 2007;35(10 (Supplement 2)):S65-S164.
175. Gidding HF, Hills S, Selvey L, Roberts LA, Johnston S. An outbreak of measles in a rural Queensland town in 1997: an opportunity to assess vaccine effectiveness. *Communicable Diseases Intelligence*. 1999;23:240-5.
176. Blake KV, Nguyen O, Capon AG. Nosocomial transmission of measles in western Sydney. *Medical journal of Australia*. 2001;175(8):442.
177. Hanna JN, Symons DJ, Lyon MJ. A measles outbreak in the Whitsundays, Queensland: the shape of things to come? *Communicable Diseases Intelligence*. 2002;26(4):589-91.
178. Kelly HA, Riddell MA, Andrews RM. Measles transmission in healthcare settings in Australia. *Medical Journal of Australia*. 2002;176(2):50-1.
179. Riddell MA, Lynch P, Jin L, Chibo D. Measles case imported from Europe to Victoria, Australia, March 2006. *Euro Surveillance: Bulletin European sur les Maladies Transmissibles = European Communicable Disease Bulletin*. 2006;11(5):E060518.2.
180. Sheppeard V, Forssman B, Ferson MJ, Moreira C, Campbell-Lloyd S, Dwyer DE, et al. The effectiveness of prophylaxis for measles contacts in NSW. *New South Wales Public Health Bulletin*. 2009;20(6):81-5.
181. Lawrence GL, MacIntyre CR, Hull BP, McIntyre PB. Measles vaccination coverage among five-year-old children: implications for disease elimination in Australia. *Australian and New Zealand Journal of Public Health*. 2003;27(4):413-8.
182. Hull B, Dey A, Mahajan D, Menzies R, McIntyre PB. Immunisation coverage annual report, 2009. *Commun Dis Intell*. 2011;35(2):132-48.
183. Ferson MJ, Robertson PW, Donovan JW. Measles immunity and immunization status in under-5-year-old children in New South Wales: a population-based study. *Journal of Paediatrics & Child Health*. 1998;34(4):339-41.
184. Causer J, Mira M, Karr M, Hueston L, Burgess M, Alperstein G, et al. Serological survey of measles and rubella immunity in Sydney preschool children. *Journal of Paediatrics & Child Health*. 2000;36(5):418-21.

185. Kelly HA, Riddell MA, Lambert SB, Leydon JA, Catton MG. Measles immunity among young adults in Victoria. *Communicable Diseases Intelligence*. 2001;25(3):129-32.
186. Hogg GG, Darlington RJ, Hogg KG, Lester R. Measles immunity and immunisation status in Australian children 1 to 4 years of age. *Journal of Paediatrics & Child Health*. 2006;42(4):165-9.
187. MacIntyre CR, Hull B, Burgess M, Gay N. Measles control in NSW divisions of general practice. *New South Wales Public Health Bulletin*. 2003;14(2):13-7.
188. Wood JG, Gidding HF, Heywood A, Macartney K, McIntyre PB, MacIntyre CR. Potential impacts of schedule changes, waning immunity and vaccine uptake on measles elimination in Australia. *Vaccine*. 2009;27(2):313-8.
189. Wang YHJ, Andrews RM, Lambert SB. Measles surveillance in Victoria, Australia. *Bulletin of the World Health Organization*. 2006;84(2):105-11.
190. Lambert S. Measles in Victoria 1992 to 1996: the importance of laboratory confirmation. *Communicable Diseases Intelligence*. 1998;22.
191. The Enhanced Measles Surveillance Working Party. Implementing a system of enhanced surveillance for measles in Victoria. *Communicable Diseases Intelligence*. 1999;23(2):51-4.
192. Heath T, Burgess M, McIntyre P, Catton M. The national measles surveillance strategy. The National Centre for Disease Control Measles Elimination Advisory Committee. *Communicable Diseases Intelligence*. 1999;23(2):41-50.
193. Brotherton J. Measles in NSW, 1991-2000. *NSW Public Health Bulletin*. 2001;12(7):200-4.
194. Durrheim DN, Speare R. Measles elimination--a case definition to enhance surveillance. *Communicable Diseases Intelligence*. 2000;24(11):329-31.
195. Lawrence G, Lambert S, Kelly H, Andrews R. Measles: how many hospitalised cases are we missing? *Communicable Diseases Intelligence*. 2001;25(3):137-40.
196. Roche P, Spencer J, Merianos A. Editorial: measles elimination in Australia. *Commun Dis Intell* 2001;25(3):141-2.
197. Kelly H, Riddell M, Heywood A, Lambert S. WHO criteria for measles elimination: a critique with reference to criteria for polio elimination. *Eurosurveillance*. 2009;14(50).
198. Kohlhaagen JK, Massey PD, Durrheim DN. Meeting measles elimination indicators: surveillance performance in a regional area of Australia. *Western Pacific Surveillance and Response Journal*. 2011;2(3):1-5.
199. Sheppeard V, Forssman B, Ferson MJ, Moreira C, Campbell-Lloyd S, Dwyer DE, et al. Vaccine failures and vaccine effectiveness in children during measles outbreaks in New South Wales, March-May 2006. *Commun Dis Intell*. 2009;33(1):21-6.
200. Shiel A, Jorm LR, Carruthers R, Fitzsimmons GJ. Cost-effectiveness of measles outbreak intervention strategies. *Australian and New Zealand Journal of Public Health*. 1998;22(1):126-32.
201. Rosewell A, Patel M, Viney K, Marich A, Lawrence GL. Impact of faxed health alerts on the preparedness of general practitioners during communicable disease outbreaks. *Commun Dis Intell Q Rep*. 2010;34(1):23-8.
202. Jayamaha J, Binns PL, Fennell M, Ferson MJ, Newton P, Tran T, et al. Laboratory diagnosis, molecular characteristics, epidemiological and clinical features of an outbreak of measles in a low incidence population in Australia. *Journal of Clinical Virology*. 2012;54(2):168-73.

Appendix B

B1.Literature Review- Measles over the last two decades in Australia

Outbreaks

| Authors | Year/Source | Location | Study Design | Results |
|-------------------------------|---|----------|----------------------|--|
| 1. Lush et al | 1995/ The NT Communicable Diseases Bulletin | NT | Outbreak report | 259 cases- that occurred in 1994. 55% cases were Aboriginal. The overall attack rate in Alice Springs region was 6.8 per 1000 population. Attack rates were 12.6 per 1000 population among Aboriginal people compared to 4.0 per 1000 population in non-Aboriginal people in Alice Spring. 8 confirmed measles cases occurred in Aboriginal infants aged < 6 months. |
| 2. Jeremijenko, Kelly & Patel | 1996/ Journal of Paediatrics & Child Health | WA | Retrospective cohort | 53 cases- 21 serological confirmed, 23 epi-linked & 9 cases clinically diagnosed. Mean age =12yrs (range 9 mths-21yrs). Index case acquired in Japan- transmission predominantly occurred at a high school (24). 91.7% of high school cases were unvaccinated. Ten cases had further complications and five were admitted to hospital. |
| 3. Gidding et al | 1999/CDI ¹⁷⁵ | QLD | Retrospective cohort | 46 cases- 10 serologically confirmed. Median age= 9yrs (range 11 mths-34yrs). Transmission occurred primarily at an education seminar during 1997. A vaccine efficacy study found that for children who had at least one dose of MMR, VE= 81.3% (84.6% for validated only). Source of infection unknown. |
| 4. Holland & Hall | 2000/CDI ⁶⁷ | SA | Outbreak report | 7 cases- all serologically confirmed. Median age= 32yrs (range 3-41yrs). Two of the cases were ambulance officers and one case was a patient assistant. Vaccination status for the three cases was unknown. Notification of all cases occurred after confirmation of diagnosis. Index had no history of recent travel. |
| 5. Hanna et al | 2000/CDI ⁵⁸ | QLD | Outbreak report | 5 cases (siblings) aged between 2.8yrs and 11.5yrs and |

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| | | | | all unvaccinated. 4/5 cases measles antigen detected in throat swabs. Symptoms of case 1 occurred in England, 12 days after leaving Sri Lanka. Four cases PCR- throat swab positive for the 'Sri Lankan genotype'. Two cases presented to a healthcare facility, one case presented three times to a general practice before being suspected of having measles. |
| 6. Lambert et al | 2000/MJA ⁶¹ | VIC | Case series using enhanced measles surveillance data in 1999. | 75 cases- 74 were lab confirmed and 1 was epi-linked. Median age was 22 years (range 10 months- 31 years old). 85% of cases were aged between 18 and 31 years. The index case recently travelled to Bali and transmission occurred primarily at the cinema complex where the index case worked. Over a third of cases required hospitalisation and 6 healthcare workers were infected. |
| 7. South Eastern Sydney PHU | 2001/CDI ⁶⁹ | NSW | Outbreak report | 5 cases- 2 cases were serologically confirmed & 2 cases measles antigen detected in throat swabs. Source of index case unknown however assumed to be acquired through occupational exposure in a health care setting. Transmission occurred primarily in a GP waiting room. |
| 8. Blake et al | 2001/MJA ⁷⁶ | NSW | Letter | 3 cases- all serologically confirmed. Index case (23 year old female) recently travelled to Hong Kong and was hospitalised with rash-associated febrile illness. Second case epi-linked to index as visited her whilst in hospital. Genotyping did not occur as attempts to culture measles virus unsuccessful in 3 patients. Third case (one-year old male) was epi-linked to index case whose sibling attended general- practice within 25 mins of index case. |
| 9. Hanna, Symons & Lyon | 2002/CDI ¹⁷⁷ | QLD | Outbreak report | 7 cases- 1 case serological confirmed, 4 cases measles RNA detected by PCR on samples taken & 1 case epi-linked. Median age= 14 years (range 11mths-19yrs). Suspected source of infection from a 16 year old female who recently travelled to Thailand who stayed with the index case. Genotyping of 5 cases identified genotype D5. |
| 10. Kelly, Riddell & Andrews | 2002/MJA ⁷⁸ | VIC, WA and NSW | Editorial | The authors discuss a number of measles transmissions in healthcare settings around the country. Predominantly, cases were acquired overseas and presented at general |

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| | | | | practices or emergency departments in hospitals. Health care professionals were among the cases that occurred in these outbreaks. The importance of outbreak control was discussed. |
| 11. Davidson et al | 2002/CDI ¹¹ | VIC | Outbreak report | 51 cases- 50 were lab confirmed. Median age= 25yrs (range 10 mths-34yrs). Transmission occurred at a number of restaurants, a nightclub, shopping centres and on public transport in 2001. One healthcare worker was infected. One case was too young to be vaccinated, 4 cases had received one dose of MMR and the remainder had no evidence of MMR vaccination. |
| 12. Fielding | 2005/ CDI ¹⁴ | SA | Outbreak report | 22 cases- all cases were lab, clinical and epi confirmed. Median age= 23yrs (range 9mths-36yrs). Transmission occurred at a concert, supermarket and at a hospital. Index case recently travelled to New Zealand. Sixty per cent of cases were unvaccinated and 27% of cases had evidence of one MMR. |
| 13. Weston et al | 2006/CDI ¹⁵ | NSW | Outbreak report | 9 cases- all cases had at least one lab test confirming measles. Median age= 24 years (range 2mths-38yrs). Index case recently travelled to Nepal via Bangkok. One case had documented evidence of one measles containing vaccine administered overseas. Nosocomial infection occurred during presentation at ED as well as in the community. |
| 14. Riddell et al | 2006/ Eurosurveillance ¹⁷⁹ | VIC | Short report | 1 case of measles imported from Europe – suggested to be linked to an outbreak in Stuttgart, Germany. No further cases were identified. Genotyping of specimen identical to a strain identified in the UK. |
| 15. Sheppeard et al | 2009/NSW Public Health Bulletin ¹⁸⁰ | NSW | Retrospective cohort | 57 cases, 1760 contacts and 553 susceptible individuals. Measles prophylaxis efficacy was calculated using data on all cases of measles notified between 1 March and 31 May 2006. Prophylaxis effectiveness (MMR/ NHIG) was 83.3%. |
| 16. Martin & Foxwell | 2009/CDI ⁷⁹ | National | Outbreak report | National outbreak data identified 78 cases between 1 Jan and 31 March 2009. Ninety three per cent of cases had not received any dose of measles containing vaccine of the cases of known vaccine status (57). Twenty two per cent of cases were acquired overseas, |

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| | | | | predominantly in young adults. |
| 17. Bowen | 2009/ Emergency Medicine Australasia ¹⁴³ | NSW | Outbreak report | The authors describe the control and prevention processes followed after an unvaccinated 15 month old presented at ED. There were 111 individuals exposed to the case of which 9 individuals were administered NHIG. Ninety-three contacts were identified as immune. |
| 18. Coleman & Markey | 2010/ Epidemiology & Infection ⁹⁵ | NT | Outbreak report | 4 cases- all serologically confirmed. Median age 14.5years (range 11-17 years). Index case flew from China-Singapore-Darwin-Melbourne. Transmission likely to have occurred during the flight from Singapore-Darwin (2 cases) and during transit (1 case). Two of the cases were fully vaccinated on ACIR records. |
| 19. Beard et al | 2010/ Western Pacific Surveillance and Response Journal ⁹¹ | VIC, QLD & NSW | Outbreak report | 9 cases- 7 cases measles antigen detected by PCR, all genotype. Two cases were serologically confirmed. Median age= 33 years (range 11-62 years). Index case administered MCV 5 days prior to flight; all other cases had no documented evidence of vaccination. Four cases likely to have become infected on flight Australia- South Africa. Other exposures include ED and GP clinic. |
| 20. Hoskins | 2011/MMWR ⁹⁴ | QLD | Outbreak report | 11 cases- 3 cases serologically confirmed; 6 cases measles RNA detected by PCR and 2 cases clinically diagnosed. Three index cases (from New Zealand) flew Singapore-Brisbane-Auckland resulted in 8 further cases. Transmission suspected to have occurred during the flight. Eight cases were unvaccinated, 2 cases vaccination status was unknown and 1 case was reported to be vaccinated. |
| 21. Flego, Sheppard & McPhie | 2011/CIDM Broad Street Pump ⁹⁶ | NSW | Outbreak report | 26 cases- 22 cases were lab and clinically diagnosed, 4 cases had clinical symptoms and were epi-linked. Age range was 8 months to 35 years. Transmission likely occurred in a high school however all cases resided in the same suburb and 46% were of Pacific Islander origin. All confirmed cases had no documented evidence of 2 MCV. |

Incidence

| Authors | Year A/Source | Location | Study Design | Results |
|----------------------|----------------------------|----------|---|---|
| 22. McIntyre et al | 2000/CDI ⁵² | National | Epi review of notification data from the NNDSS 1 Jan 1993 to 31 Dec 1998 and hospitalisation data using AIHW National Hospitalisation Morbidity data for 1 July 1993 to 30 June 1998. | <p>Between 1993 and 1998 the annual notification rate was 11.4 per 100,000 population. During this period there were 12,404 notified cases of measles. The notification rate was highest in the 0-4 year age group (45.4 per 100,000 population) followed by the 5-14 year age group (31.8 per 100,000 per 100,000 population). Notification rates were highest in the NT (51.7 per 100,000 population).</p> <p>There were 2223 hospitalisations due to measles and the average annual hospitalisation rate of 2.5 per 100,000 population. 20% of hospitalisations had complications due to measles. Hospitalisation rate during this period was highest in the 0-4 year age group (14.6 per 100,000 population).</p> |
| 23. McIntyre et al | 2002/CD I ⁵³ | National | Epi review of notification data from the NNDSS 1 Jan 1999 to 31 Dec 2000 and hospitalisation data using AIHW National Hospitalisation Morbidity data for 1 July 1998 to 30 June 2000. | <p>Between 1999 and 2000 the notification rate for measles was 0.9 per 100,000. There were 336 notified cases during this period. Notification rates were highest in the 0-4 year age group (4.3 per 100,000 population) and 15-24 year age group (2.0 per 100,000) during this period. Notification rates were highest in Victoria, all states and territories reported cases of measles during this period.</p> <p>During 1998/1999 to 1999/2000, there were 145 hospitalisations of which complications occurred in 19%. Hospitalisation rates were highest in the 0-4 year age group.</p> |
| 24. Brotherton et al | 2004/CD I ⁷⁰ | National | Epi review of notification data from the NNDSS 1 Jan 2001 to 31 Dec 2002 and hospitalisation data using AIHW National | <p>Between 2001 and 2002 the notification rate for measles was 0.4 per 100,000 population. Measles notifications- 2000 (n=107), 2001 (n=139) and 2002 (n=32). Notification rates were highest in age groups 0-4 years and</p> |

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| | | | Hospitality Morbidity data for 1 July 2000 to 30 June 2002. | <p>15-24 years during this period. Victoria had the highest notification rate (1.7 per 100,000) and all other states reported measles cases. Both ACT and NT did not report any measles cases during this period.</p> <p>During 2000/2001 and 2001/2002 there were 105 hospital separations due to measles and 11% of these led to complications due to measles. Hospitalisation rates were highest in the 0-4 year age group.</p> |
| 25. Brotherton et al | 2007/CDI ⁸³ | National | Epi review of notification data from the NNDSS 1 Jan 2003 to 31 Dec 2005 and hospitalisation data using AIHW National Hospitality Morbidity data for 1 July 2002 to 30 June 2005. | <p>Between 2003 and 2005 the notification rate for measles was 0.25 per 100,000 population. Measles notifications- 2003 (n=93); 2004 (n=45); 2005 (n=10). Notification rates were highest in children < 5 years and individuals aged 15-54 years of age.</p> <p>Notification rates were highest in SA and the NT (0.65 per 100,000 and 0.67 per 100,000, respectively).</p> <p>During 2002/2003 to 2004/2005, there were 94 hospital separations and 21% of separations had complications due to measles. Hospitalisation rates were highest in individuals < 5 years old and 20-35 years old groups.</p> |
| 26. Chiu et al | 2010/CDI ⁸⁵ | National | Epi review of notification data from the NNDSS 1 Jan 2005 to 31 Dec 2007 and hospitalisation data using AIHW National Hospitality Morbidity data for 1 July 2005 to 30 June 2007. | <p>Between 2006 and 2007 the notification rate for measles was 0.33 per 100,000 population. Of the 137 cases, 93% were confirmed cases. Measles notifications- 2005 (n=10), 2006 (n=125) and 2007 (n=12). Notification rates were highest in < 5 years of age. Between 2006 and 2007, measles cases were notified in all jurisdictions excluding NT.</p> <p>138 hospital separations due to measles occurred between July 2005 and June 2007. Hospitalisation rates were highest in children < 5 years of age in this period. Complications due to measles occurred in 16% of hospital separations.</p> |

Immunisation Coverage

| Authors | Year/Source | Location | Study Design | Results |
|--------------------|----------------------------|----------|--|---|
| 27. McIntyre et al | 2000/CDI ¹² | National | Epi review using data from the ABS survey in 1995 and ACIR data from 1996-1998. ACIR coverage estimates for MMR1 assessed at 2 years of age (by 3 month cohort born in children born 1 January 1996 to 31 March 1996). The vaccination status of each cohort is estimated at 12 months and 24 months of age. Trends in MMR coverage used four cohorts of 2 year olds by jurisdiction. | MMR coverage was found to increase in all jurisdictions. QLD vaccine coverage estimate was greater than 95 % whilst the rest of the states and territories were below the target of 95% coverage. Underestimates of ACIR coverage is likely by at least 5%. |
| 28. McIntyre et al | 2002/CDI ¹¹ | National | Epi review using data from ACIR data from 31 March 1999 to 30 September 2001. ACIR coverage estimates for MMR1 assessed at 2 years of age (by 3 month cohort born in children born 1 January 1998 to 30 September 2000). Trends in MMR coverage used four cohorts of 2 year olds by jurisdiction. | Vaccination coverage of MMR1 at 2 years of age increased over the period with South Australia being the only jurisdiction to reach the target of 95% coverage (2001). |
| 29. Lawrence et al | 2003/ ANZJPH ¹⁸ | National | Cross-sectional study of all children born 1 Oct to 31 Dec 1995 who were registered on the ACIR on 4 May 2001. Parents of a sample of children with no record of MMR2 were phone interviewed to determine reasons for non-uptake of MMR2 and to assess under-reporting. | Parents of 22% of children registered on the ACIR as not having MMR2 were reported to have been immunised before 5 years of age and 42% of children by 5.5 years of age. Reports from parents identified under-reporting in the ACIR data and vaccine coverage was 4.3% higher (5 year olds) and 8.2% (5.5 year olds) than ACIR coverage estimates. Correction of coverage estimates resulted in 93% of the group being immunised (MMR2). Lack of knowledge of the MMR vaccine schedule was the most cited reasons to non-uptake of MMR2. |

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| 30. Brotherton et al | 2004/CDI ¹⁰ | National | Epi review using data from ACIR data from 31 March 2001 to 31 December 2003. ACIR coverage estimates for MMR1 assessed at 2 years (by 3 month cohort born in children born 1 January 1999 to 31 March 2001). Two years of MMR2 coverage data for six year milestone of age were available between 31 March 2002 and 31 December 2003 (by 3 month cohort born in children born 1 January 1996 to 31 December 1997). | Between 2001 and 2003, vaccine coverage remained stable and approximately 93%. Vaccination coverage of MMR2 at age 6 years was observed to be steady (slight increase) during this period hovering towards 85%. |
| 31. Brotherton et al | 2007/CDI ³³ | National | Epi review using data from ACIR data from 31 March 2003 to 31 December 2005. ACIR coverage estimates for MMR1 assessed at 2 years (by 3 month cohort born in children born 1 January 2001 to 31 March 2003). MMR2 Coverage data for six year milestone was estimated between 31 March 2003 and 31 December 2005 (by 3 month cohort born in children born 1 January 1997 to 31 December 1999). | MMR1 coverage estimates at 24 months of age remained relatively stable during this period and was below the target of 95% coverage. Timeliness of MMR1 was measured by jurisdiction for the cohort born from 1 January 2003 to 31 March 2003. Timeliness in WA and the NT were observed to be the poorest in uptake of MMR1. By 18 month, all jurisdictions appear to have the same cumulative coverage. MMR2 coverage also remained steady with coverage being approximately 85% during this period. |
| 32. Hull et al | 2009/CDI ³⁸ | National | Epi review using 2007 data from ACIR data. ACIR coverage estimates for MMR1 assessed at 2 years and MMR2 at 6 years of age. For 24 month milestone (by 3 month cohort born in children born 1 January to 31 December 2005) | 94.1% of children on the ACIR had MMR1 by 24 months of age. Tasmania and the NT achieved the 95% target whilst WA had the lowest coverage (93%). MMR2 coverage at 6 years of age was lower with 88.4% of children having been vaccinated. Victoria was the only state to achieve higher than 90% coverage (90.9%). |

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| | | | and six year milestone (by 3 month cohort born in children born 1 January to 31 December 2001). | Trends in vaccination coverage found that there was a steady increase in MMR1 vaccine uptake between 31 Mar 1998 and 30 Sep 2007. Whereas there was a sharp increase in MMR2 uptake mid-2006. |
| 33. Hull et al | 2010/CDI ⁽⁹⁾ | National | Epi review using 2008 data from ACIR data. ACIR coverage estimates for MMR1 assessed at 2 years and MMR2 at 5 years of age. For 24 month milestone (by 3 month cohort born in children born 1 January to 31 December 2006) and five year milestone (by 3 month cohort born in children born 1 January to 31 December 2003). | MMR1 coverage in Australia was found to be 94% with the ACT and NT being the only jurisdictions to reach the target of 95% coverage. The lowest coverage was observed in WA (90.8%). MMR2 coverage in Australia was found to be 79.8% with ACT having the highest coverage of 85.9% and SA the lowest (74.7%). MMR1 coverage trend appears to be steady since mid-2002 whilst there was a sharp decrease in MMR2 coverage at the end to 2007 which was due to the change in assessment age. |
| 34. Hull et al | 2011/CDI ⁽¹⁰⁾ | National | Epi review using 2009 data from ACIR data. ACIR coverage estimates for MMR1 assessed at 2 years and MMR2 at 5 years of age. For 24 month milestone (by 3 month cohort born in children born 1 January to 31 December 2007) and five year milestone (by 3 month cohort born in children born 1 January to 31 December 2004). | MMR1 coverage was 93.8% in Australia and no jurisdiction reached the 95% coverage target. WA had the lowest coverage with 92.9% uptake. MMR2 coverage was 83.2% in Australia and SA had the lowest coverage of 79.3%. |

Population Immunity

| Authors | Year/Source | Location | Study Design | Results |
|---------------|-----------------|----------|---------------------------------|--|
| 35. Ferson et | 1998/Journal of | NSW | Population based seroprevalence | 62.4% of the 689 study participants provided a blood |

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| al | Paediatrics & Child Health ¹⁸³ | | survey using two different enzyme immunoassays on plasma in children 1-4 years of age between February to March 2005. | sample and of these, adequate plasma remained for 347 subjects. 80.4% of children were immune. |
| 36. Causer et al | 2000/ Journal of Paediatrics & Child Health ¹⁸⁴ | NSW | Analysis of a clustered sample of sera in children 18 months- 5 years. Seroprevalence was measured using enzyme immunoassays between 1992 and 1994. | Adequate plasma remained for 580/726 children whose parents agreed to participate in the study. Measles immunity was found to be 88.8% and documented evidence of measles in 88.4% of children. 91.6% of children with documented evidence of measles vaccination had detectable measles antibody. |
| 37. Gidding & Gilbert | 2001/CDI ¹² | National | Analysis of a clustered sample of sera collected opportunistically between July 1996 and November 1998. Seroprevalence was measured using enzyme immunoassays. | 2126 sera samples in 19-49 year olds. Immunity was highest in subjects born before 1968 (98.3%). Immunity was lowest in subjects born in 1994-1998 (83.6%) and in subjects born in 1974-1980 (88.9%). |
| 38. Gilbert et al | 2001/ Epidemiology and Infection ⁶² | National | Analysis of a clustered sample of sera collected opportunistically before and after the 1998 Australian Measles Control Campaign. Samples were collected 2 years before the campaign and between January and May 1999. | 4400(1-49 years) and 3000 (1-18 years) samples were collected before and after the campaign, respectively. Measles immunity in those 1-18 years increased from 85% before, to 90% after the campaign. The greatest increase was in preschool (7%) and primary school (10%) children. |
| 39. Kelly et al | 2001/CDI ¹⁸⁵ | VIC | Comparative analysis of blood samples in healthy subjects aged 18-30 years and 312 sera samples stored at VIDRL following diagnostic testing. Sera from health subjects were collected in March 1999. Immunity was measured using a standard enzyme immunoassay. | No significant difference in measles immunity between healthy adults and subjects with sera stored were observed. 88.4% of individuals born in 1968 to 1974 were found to be immune to measles whilst 74.1% born in 1975 to 1981 were immune to measles. |
| 40. Hogg et al | 2006/ Journal of Paediatrics & Child Health ¹⁸⁶ | National excluding NSW | Analysis of a clustered sample of sera of children aged 1-4 years. Samples were collected between February and April 1995. Immunity was measured using an enzyme | 923 subjects provided blood samples and 86% of children were immune to measles. Of those who were reported to have been immunised against measles, 91% tested seropositive. |

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| 41. Kelly et al | 2007/ BMC Public Health ⁷³ | VIC | immunoassay. Population based seroprevalence survey in young adults (20-34 years old) using enzyme immunoassays in 2002. Results were compared to the 1999 Victorian state serosurvey. Evaluation of the young adult MMR campaign compared results from the Victorian results of the two national serosurveys in 1996-1999. | No significant change was observed in immunity in young adults following the young adult MMR campaign (83.9% before and 85.5% after the campaign) in the state serosurveys. The Victorian component of the national serosurveys found a significant decline in immunity (91% before and 84.2% after the campaign). |
|-----------------|---------------------------------------|-----|--|---|

Estimation of R

| Authors | Year/Source | Location | Study Design | Results |
|---------------------|--------------------------------------|----------|---|--|
| 42. MacIntyre et al | 2002/IJID ⁶³ | National | Mathematical modelling to calculate R used serosurvey results before and after the Measles Control Campaign from subjects 1-49 years of age and vaccine coverage estimates. | Before the campaign R was estimated to be 0.90 After the campaign R was estimated to be 0.57 ACIR data suggested that R would exceed 1 by 2007-2008 nationally and sooner in some regions of Australia. |
| 43. MacIntyre et al | 2003/ NSW PH Bulletin ¹⁸⁷ | NSW | Mathematical modelling of vaccine coverage was used to predict measles control in 2001 for the doses given at 12 months and four years by divisions of general practice. Serosurvey data was used to estimate susceptibility. Susceptibility in some age-specific cohorts was estimated by coverage and vaccine efficacy. The average, best and worst R values over time were calculated by division of | By the age of 5, 11 % of children had not received a dose of MMR, and 35% had only received a single dose. In inner Sydney, the average R value was projected to exceed 1 in 2003 compared to the average R values in outer Sydney and South and West NSW exceeding 1 in 2005. Northern NSW was observed to have the best measles control with the average R value estimated to exceed 1 in 2006. |

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| | | | general practice if vaccination coverage remained the same. | |
| 44. Becker et al ¹¹⁷ | 2005/ANZJPH | VIC | Mathematical modelling was used to estimate the probability of R exceeding 1 using Poisson offspring and geometric distributions. Outbreaks that were notified between 1998 and 2003 were used. | <p>The probability that R exceeds 1 was found to be 0.044 under the geometric model and 0.026 under the Poisson offspring model.</p> <p>Individuals aged 19 to 32 years and children < 2 years were identified as the most susceptible populations.</p> |
| 45. Gidding et al ¹²² | 2007/ Vaccine | National | Mathematical modelling of vaccine coverage was used to calculate R and predict R until 2012. 2002 serosurvey data was used to estimate susceptibility. Comparison of serosurvey results were conducted with previous serosurveys. Susceptibility of new birth cohorts were projected using vaccine coverage. | <p>2002 population seroprevalence was found to be significantly lower (93.9% versus 95.0%; $p = 0.004$) than the estimate from the first serosurvey (1996-1999).</p> <p>R was calculated to be 0.69, predicted to remain below 0.8 between 2003 and 2012 however an upward trend was predicted to occur after 2010.</p> |
| 46. Wood et al ¹⁸⁸ | 2009/ Vaccine | National | Modelling was used to estimate R using a contact matrix based on UK data to include patterns of contact in the community in addition to serosurvey data and vaccine coverage data if MMR2 was moved from 4 years to 18 months. The effect of this shift was modelled on population susceptibility. | <p>R was predicted to remain below 1 until 2028 and be slightly lower if MMR2 is given at 18 months.</p> <p>If 6% of vaccinated who initially seroconvert and then became susceptible after 10 years, R was estimated to exceed 1 past 2015 for both schedules.</p> <p>R was estimated to remain below 1 until 2028 if the one MMR dose coverage of 96%.</p> <p>Measles susceptibility was predicted to reduce considerably in the 2-4 year age group and reduce slightly in the overall population if the MMR2 was brought forward to 18 months. The model suggests that the long-term trend for susceptibility is increasing.</p> |

Circulating measles genotype

| Authors | Year/Source | Location | Study Design | Results |
|-----------------|---|------------------------|---|--|
| 47. Chibo et al | 2000/ Journal of General Virology ⁶⁴ | VIC | Molecular epidemiological study conducted between 1973 and 1998. | 35 wild-type measles viruses were identified however the continuous replacement of genotypes without temporal overlap suggests that transmission of an indigenous genotype of measles in Australia has ceased. |
| 48. Chibo et al | 2002/ Emerging Infectious Disease ⁶⁵ | QLD & VIC | Short report of a novel genotype identified in Australia in 1999. | A novel genotype of measles (G3) was identified in 1999 and found to be circulating in Queensland. Importation of this genotype was also observed following measles cases among refugees from East Timor. |
| 49. Chibo et al | 2003/ Virus Research ⁶² | VIC, NSW, QLD, NT & WA | Molecular epidemiological study conducted between 1999 and 2001. | 9 different genotypes of measles were identified including 1 new genotype. There was no evidence of a circulating indigenous genotype in Australia. Young adults appeared to be the highest risk of infection. Most index cases were found to acquire infection from overseas. |

Discard rate

| Authors | Year/Source | Location | Study Design | Results |
|-----------------------------|---|----------|--|---|
| 50. Wang, Andrews & Lambert | 2006/ Bulletin of WHO ¹⁸⁹ | VIC | Epidemiological review of measles notifications between 1998 and 2003. Discarded notifications during epidemic and interepidemic periods were used to calculate discard rates. | Discarded measles notifications were estimated to be 41% (422) during interepidemic periods and 59% (608) during epidemic periods. Highly sensitive algorithms of sentinel measles cases were developed to detect sentinel cases during interepidemic periods potentially saving the resources required to perform enhanced surveillance on a high number of discarded notifications. |
| 51. Wang et al | 2007/ Epidemiology & Infection ¹²⁷ | VIC | Epidemiological review of measles notifications between 1998 and 2003. | Seventy two per cent of measles notifications were found to be discarded after testing. The median annual discard rate was calculated to be 2.9 per 100,000. The annual rate of discarded notifications in Victoria was above the minimum recommended standard. The annual rate of discard was higher during epidemic periods compared to interepidemic periods and infants < 1 years of age. |

Surveillance

| Authors | Year/Source | Location | Study Design | Results |
|---|--------------------------|----------|---|--|
| 52. Ferson et al | 1995/ MJA ¹⁴ | NSW | Case survey between December 1990 and August 1993 | 49 cases that had no/not yet been serologically confirmed but clinically diagnosed with measles were assessed. A clinical diagnosis was found to have a false positive rate of 51%. Of subjects confirmed with measles, a cough and febrile on the day of rash onset were more likely than individuals with no definite diagnosis. |
| 53. Lambert | 1998/ CDI ¹⁹⁰ | VIC | Epi review looking at notification and laboratory testing data for measles and public hospital discharge codes between 1992 and 1996. | Notification data- The notification rate of measles decreased in the five year period. Notification rates were highest for children below the age of five years. Lab confirmation was received for 16.2% of notifications. Lab testing- 11% of tests performed for measles were positive with the highest proportion positive in 1993 and 1994. Hospital data- 102 discharges with a primary diagnosis relating to measles |
| 54. The Enhanced Measles Surveillance Working Party | 1999/CDI ¹⁹¹ | VIC | Surveillance summary of the implementation of an enhanced surveillance system for measles in 1997-1998. Attempts to interview all notified case of measles (or guardians) through a structured telephone questionnaire were made. Serological samples were collected at the case's home by a paediatric phlebotomist. | There were 317 notifications of measles during this time period. After the introduction of the phlebotomy service, serological confirmation for all notifications increased from 69% (July – Dec 1997) to 90% (July-Dec 1998). The median delay between illness onset and notification was 7 days and the median time from notification to specimen collection was 1 day (July 1997-December 1998). Data on immunisation status was obtained in 97% of the 317 notifications of measles. |
| 55. Heath et al | 1999/CDI ¹⁹² | National | Surveillance plan | To prepare for measles elimination, a number of recommendations were made including: <ul style="list-style-type: none"> - Revising control targets (vaccination coverage and population immunity) to align with ability to achieve elimination - Develop standardised, sensitive and simple case |

| | | | | |
|-----------------------|--------------------------------------|----------|--|---|
| | | | | <ul style="list-style-type: none"> definitions All suspected measles cases should undergo serological testing. Positive serological results from a sporadic case should be confirmed at a reference laboratory. Specimens to culture at least 2 cases in an outbreak should occur to allow for genotyping Uniform case investigation and consistent data collection (including vaccination status), investigation of measles outbreaks Active surveillance and standard indicators to monitor the quality of surveillance data Enhancing AEFI surveillance Conducting national serological surveys |
| 56. Lambert et al | 2000/ MJA ¹⁵ | VIC | Case series using enhanced measles surveillance data between July 1997 and 1998 (inter-epidemic period). | In the six months preceding July 1997, 23% of notified measles cases had sera collected. Following the employment of a paediatric phlebotomist, 81% of measles cases had their sera collected (July 1997-Dec 1998). Of these samples, 19% were lab confirmed measles; the remainder were found to be human parvovirus or rubella. This report highlighted the importance of a lab confirmed diagnosis of measles particularly during an inter-epidemic period. |
| 57. Brotherton | 2000/ NSW PH Bulletin ¹⁹³ | NSW | Epi review of measles notifications and hospital separations between 1991 and 2000 | 6390 measles cases were reported during the 10-year period of which 18.5% were lab confirmed. The proportion of lab confirmed cases as lowest in 1991 (4%) and highest in 2000 (61%). The highest number of notifications occurred in 1993 (2348) and the lowest in 1999 (32). Most notifications were reported in children less than 5 years of age. 431 Hospitalisations occurred during calendar year from 1994 to 1999 and 3 deaths were recorded. |
| 58. Durrheim & Speare | 2000/CDI ¹⁹⁴ | National | Editorial | The authors note the importance of enhanced surveillance of measles during a measles elimination phase. Specifically, a standardised, highly sensitive case definition that is not ambiguous. |
| 59. Turnbull et al | 2001/ Bulletin of WHO ⁷⁹ | National | Evaluation of the 1998 Measles Control Campaign. Overall coverage of MMR was measured in | Over 1.33 million children (5-12 years old) were vaccinated at school. An estimated 1.7 million doses were administered during the campaign. Prior to the campaign, |

| | | | | |
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| | | | <p>children < 7 years of age using ACIR data. ACIR data was also used to identify pre-school children whose first dose of MMR was overdue and reminder letters sent. Effect of letter measured by checking ACIR data and random telephone interviews. A cluster sampling method of primary schools was also used to measure coverage.</p> <p>Data on adverse events following immunisation (AEFIs) during the campaign were obtained from three sources. Immunity was estimated by serosurveys conducted before and after the campaign. Incidence of disease was measured using NNDSS data immediately after the campaign (Jan-June 1999)</p> | <p>84% of school children were immune to measles and after the campaign, this increased to 94%. Among pre-school children, 82 % were immune to measles prior to the campaign and 89% were immune after the campaign. 89 AEFIs were reported during the campaign (5 per 100 000 doses). A marked reduction in measles incidence immediately after the campaign was observed in the age groups targeted.</p> |
| 60. Lawrence et al | 2001/ CDI ¹⁰⁵ | VIC | <p>Surveillance report.</p> <p>Data from the Victorian Inpatient Minimum Dataset between 1 Jan 1997 and 30 June 1998 was compared to the Victorian enhanced measles surveillance database. Hospital case notes of measles cases hospitalised however not entered in the surveillance dataset were examined to determine whether these cases met a lab or clinically diagnosis of measles.</p> | <p>1 case was lab confirmed and 2 cases were clinically diagnosed with measles. These patients were not notified to the health authorities highlighting inadequacies in notification of measles by hospital staff.</p> |
| 61. Gidding | 2005/Epidemiology Infection ¹⁰⁸ | National | <p>Epi review of measles surveillance data between 1993 and 2002</p> | <p>Reduction in measles notification and hospitalisation rates started to decline following the introduction of the second dose of MMR. A peak was noted to have occurred in 1997 due to an outbreak. Notification rates among 10-19 year olds (targeted in the campaign) declined the most and this</p> |

| | | | | |
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| | | | | was also reflected in hospitalisation rates. In 1998, the age of second dose was lowered to 4 years and notification and hospitalisation rates were further reduced. The highest notification rates were observed in children < 5 years however notifications among young adults were increasing. |
|--|--|--|--|---|

Elimination


| Authors | Year/Source | Location | Study Design | Results |
|-------------------------------|---------------------------------------|----------|--------------|---|
| 62. Roche, Spencer & Merianos | 2001/CDI ¹⁹⁶ | National | Editorial | The authors concluded that if the criterion for elimination of measles was based on the end of an endemic circulating genotype of measles, Australia has achieved measles elimination. |
| 63. Kelly et al | 2009/ Eurosurveillance ¹⁹⁷ | National | Perspective | Key elimination criteria are considered by the authors- 1. Molecular evidence that no circulating endemic genotype of measles for at least one year 2. Vaccine coverage of one dose MCV is maintained at 95%. The authors propose that elimination status should be reviewed annually and that four principles should guide the development of formal declaration of measles elimination: <ol style="list-style-type: none"> 1. Elimination criteria should be met by countries that have eliminated measles 2. Elimination of measles should not be defined by quality surveillance criteria 3. Elimination criteria should quality surveillance criteria 4. Elimination criteria should be standard across WHO regions unless for good reason |
| 64. Heywood et al | 2009/ Bulletin of WHO ⁶ | National | Epi review | The authors describe the WHO criteria for measles elimination and demonstrate that Australia is not fulfilling these criteria. They argue however that specific criteria have been met to justify the formal declaration of measles elimination and provide evidence to support this. |
| 65. Kohlhausen, Massey | 2011/ WPSAR ¹⁹⁸ | NSW | Surveillance | 63 notifications were identified in the region and six of the |

| | | | | |
|------------|--|--|---|--|
| & Durrheim | | | Project between June 2006 and June 2008 | ten measles indicators established by the WPR of WHO for elimination were met. Three were not applicable and two doses of MCV coverage was found fell below the > 95% indicator (91.9%). |
|------------|--|--|---|--|

Vaccine Effectiveness

| Authors | Year/Source | Location | Study Design | Results |
|---------------------|----------------------------|----------|--|---|
| 66. Patel & Lush | 1998/ANZJPH ¹⁹⁴ | NT | Retrospective cohort | Vaccine effectiveness was measured during an outbreak in Alice Springs in 1994. There were 109 individuals that were eligible (children aged 9 months and 10 years residing in a particular remote community) to participate in the study. 108 children were immunised and 7 developed measles. Overall vaccine effectiveness was 93.5% (95% CI 86.7%-- 96.8%). Vaccine effectiveness was 92.2% (95% CI 83.2--96.4%) in children vaccinated < 12 months compared to 96.8% (95% CI 77.8--99.5%) in children vaccinated > 12 months. However, this difference was not statistically significant |
| 67. Sheppeard et al | 2009/CDI ¹⁹⁹ | NSW | Retrospective cohort | Vaccine effectiveness was measured during a NSW outbreak in 2006. There were 33 cases aged 12 months to 7 years and of these, 6 received at least one dose of MMR. The age adjusted vaccine effectiveness for one dose of MMR was 96% (77.8%-- 99%). |
| 68. Shiell et al | 1998/ANZJPH ²⁰⁰ | National | Decision-analytic model to estimate cost effectiveness of outbreak control procedures. | In a hypothetical scenario of an outbreak occurring in a primary school (5--10 years of age) setting of 500 students and their younger siblings, 6 control strategies and their cost-effectiveness were examined. Vaccinating only unvaccinated students would lead to \$32.90 cost to prevent one case whilst if you were to also vaccinate siblings all siblings > 6 months irrespective of vaccination status, the cost per case prevented was estimated at \$6795.70. Vaccinating all school children irrespective of vaccination status would cost \$836.00 to prevent one |



| | | | | |
|--------------------|--|-----|---------------------------------|---|
| 69. Rosewell et al | 2010/CDI ²⁰¹ | NSW | Retrospective cohort | case. 328 GPs participated in the study to measure awareness of a measles outbreak and the impact of receiving a faxed alert from the health department or the Australian General Practice Network. GPs were more likely to be aware of a measles outbreak when sent a fax alert by the health department (RR 1.18; 95% CI 1.02—1.38) and report that susceptible staff were offered MMR vaccine during the outbreak (RR 1.55; 95% CI 0.99—2.45) than those not sent an alert. They were also more likely to isolate patients with suspected measles (RR 3.30; 95% CI 1.83—5.97) and notify suspected cases (RR 4.26; 95% CI 1.93—9.41). |
| 70. Jayamaha et al | 2012/Journal of Clinical Virology ²⁰² | NSW | Retrospective descriptive study | Between February and May 2011, 34 individuals were suspected of measles and 16 cases were confirmed at SEALS. The mean age was 22.4 years (range 1–35 years). 11 of the cases were young adults. Two cases were acquired overseas there was one hospital based cluster whilst the remaining were community based. The most common genotype was D9 (11 cases). One case was fully vaccinated by age. |

Australian National University 

Transmission of measles in an era of elimination in Australia

May Chiew
Master of Philosophy (Applied Epidemiology) Scholar

Co-authors: Heather Gidding, Adis Dey, Stephanie Davis, Peter McIntyre

Background: Measles

- Paramyxovirus
- Highly infectious
- Clinical signs- fever, cough, coryza, conjunctivitis, maculopapular rash
- Complications
- Rare disease in Australia
- Elimination since 2005¹






¹ <http://www.health.gov.au/immunisation/2005>



Background: Reproduction number

- Elimination
- Eradication
- Reproduction number (R)
 - $R > 1$: Epidemic
 - $R = 1$: Endemic
 - $R < 1$ maintained: Elimination



Measles case definition

Laboratory definitive evidence
OR
Clinical evidence (generalised maculopapular rash lasting three or more days and fever at the time of rash onset and cough or coryza or conjunctivitis or Koplik spots) and epidemiological evidence



Aim

To examine the current epidemiology of measles and to provide evidence that measles elimination is being maintained in Australia

Methods

- Measles notifications, National Notifiable Disease Surveillance System (NNDSS)
 - Trends (2000-2011)
- Estimation R
 - Data fields used
 - Importation status (NNDSS 2008-2011)
 - Outbreak reference number (NNDSS 2009-2011)
 - Algorithms developed where data fields missing

Methods- Estimation of R

1. Proportion of imported cases (2008-2011)

$$R = 1 - \frac{\text{imported number of cases}}{\text{total number of cases}}$$

2. Distribution of outbreak size (n) (2009-2011)

$$\text{Probability}(n) = \frac{R^{n-1} (1-R)^2}{(n-1)!}$$

3. Distribution of generations of spread (n) (2009-2011)

$$\text{Probability}(g) = e^{-R} \frac{R^g}{g!}$$

Dr Sarah Hay, ANU School of Biomedicine, 2016



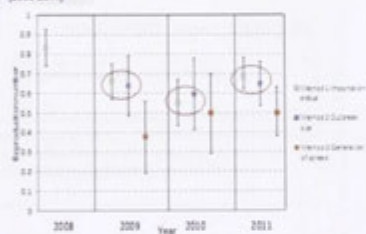
ncirs
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Immunisation Research and
Surveillance

Results: Measles notification rates by year of diagnosis, 2000-2011



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Results: Estimation of the reproduction number (R) of measles by year (2008-2011)



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Surveillance

Results: Estimation of the reproduction number (R) of measles (2009-2011)



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Surveillance

Interpretation of findings

- Elimination maintained, low notification rates
- Similarities of R estimates by the three methods

Limitations

- Underreporting
- Data quality
- Assumptions to estimate R



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Surveillance

Public health implications/Conclusions

- Evidence of sustained elimination
- Surveillance systems- a tool for monitoring elimination
- Data completeness needs to improve
- World Health Organization global eradication goal



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Surveillance

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- Dr Martyn Kirk (Australian National University)
- Commonwealth Department of Health and Ageing
- National Centre for Immunisation Research and Surveillance
- MAE Scholars 2012
- Measles elimination working group, Australia



Transmission of measles in an era of elimination in Australia; 2000-2012



Australian
National
University



May Chiew^{1,2}, Heather Gidding^{1,3}, Aditi Dey¹, James Wood³, Nicolee Martin⁴, Stephanie Davis², Peter McIntyre¹

1. National Centre for Immunisation Research and Surveillance, NSW; 2. Australian National University, ACT; 3. University of NSW, NSW; 4. Department of Health and Ageing, ACT

Background

In 2005, the World Health Organisation Regional Office for the Western Pacific (WPRO) set 2012 as the target year to eliminate measles in the region.¹ Based on several criteria set by WPRO, including maintenance of a reproduction number (R) below 1, indigenous transmission of measles was argued to have ceased in Australia since 2005.² However, other WPRO criteria, such as very low incidence and meeting specific surveillance criteria have not been met.

Aim

To examine recent trends in measles notifications and estimate R using routinely collected surveillance data in order to provide evidence that measles elimination is being sustained in Australia.

Methods

Measles surveillance data obtained from the National Notifiable Disease Surveillance System were used to:

- Examine trends (2000-2012) in notifications
- Estimate R (2009-2011) based on: 1) Proportion of imported cases; 2) Distribution of outbreak sizes (and a sensitivity analysis of outbreaks ≥ 3 cases); 3) Distribution of generations of spread

R , the average number of secondary cases from an infectious case, can be used to monitor measles elimination. R is required to be maintained below 1 to meet criteria for elimination. Completeness of data fields required to estimate R were assessed and where incomplete, algorithms were developed to determine if these cases belonged to another outbreak. Analyses were performed using the statistical software Stata[®] version 12 and Matlab[®].

Results

Between 2009 and 2011, there were 367 notifications of measles, 35% ($n=128$) of cases were acquired overseas. Only 77% ($n=283$) of cases had complete information about whether they belonged to an identified outbreak. Following an algorithm to identify possible clusters, a further 5% ($n=19$) were identified to be part of an outbreak. Overall, there were 55 outbreaks (range 2-25 cases) and 78 sporadic cases during 2009-2011. The longest duration of an outbreak was estimated to be 7 generations (67 days).

Figure 2. R estimates remained below 1 for all three methods, 2009-2011



Figure 1. The fluctuating annual measles notification rates in Australia, 2000-2012

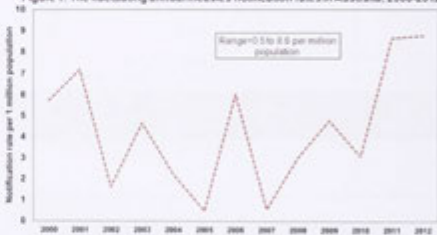


Table 1. R estimates remained below 1 for all three methods by individual year, 2009-2011

| Methods | 2009 | | 2010 | | 2011 | |
|---|------|-------------------------|------|-------------------------|------|-------------------------|
| | R | 95% Confidence Interval | R | 95% Confidence Interval | R | 95% Confidence Interval |
| Proportion of imported cases | 0.66 | 0.57-0.75 | 0.55 | 0.43-0.67 | 0.68 | 0.62-0.75 |
| Distribution of outbreak sizes | 0.65 | 0.49-0.80 | 0.59 | 0.41-0.79 | 0.65 | 0.53-0.76 |
| Distribution of outbreak sizes ≥ 3 cases | 0.79 | 0.57-1.00 | 0.65 | 0.40-0.90 | 0.62 | 0.47-0.76 |
| Distribution of generations of spread | 0.38 | 0.19-0.56 | 0.50 | 0.29-0.70 | 0.50 | 0.38-0.63 |

Conclusion

Even though Australia did not meet the WPRO criteria for measles elimination during this period (annual notification rate was > 1 case per million for most years and other required surveillance data such as testing discard rates are not routinely available), R was shown to be substantially below 1 by a range of different methods, supporting the contention that elimination continues to be maintained. This is consistent with the 2002 serosurvey results which estimated R to be 0.69.³ These results provide evidence that measles elimination is being maintained in Australia and are further supported by high measles vaccine coverage rates and the absence of an endemic circulating genotype in Australia for many years.²

Acknowledgements

NCIRS is funded by the Australian Government Department of Health and Ageing. Canberra. M Chiew is a scholar of the Master of Philosophy (Applied Epidemiology) degree at the Australian National University. H Gidding is funded by a NH&MRC postdoctoral research scholarship.

References

1. Resolution WHA60.88. 2005. Manila. WHO Regional Committee for the Western Pacific. 2005; 214-5.
2. Heywood, et al. Bull World Health Organ 2009; 87: 64-71.
3. Gidding H, et al. Vaccine 2007; 25: 3076-3080.



Health

Western Sydney
Local Health District

Measles Suspected Source of Infection Questionnaire

Paediatric Hospital Emergency Department

Western Sydney

Friday 11 May, 2012

SECTION 1: CONTACT DETAILS

Surname: _____

First name: _____

Telephone: _____

INTERVIEWER SCRIPT:

"Good morning/afternoon. My name is _____ and I'm calling from the Parramatta public health unit in Sydney. I was hoping to speak with the parents/guardian of _____. I am calling in regards to your child being at the emergency department at the Children's Hospital at Westmead in May. Records from the emergency department indicate _____ was present on 11th May. A number of children who were at the ED on the same day as _____ became infected with measles. We are trying to investigate the source of infection and whether there might have been other children who became infected with measles. We would like to ask you a few questions, it should take approximately ten minutes to complete. All the information we collect is confidential and only authorised public health staff will have access to this information. Would it be possible for you to answer our questions?"

* If parent/guardian unavailable, ask what is the best time to call back _____

Verbal consent given for interview:

Yes ☐

No ☐

SECTION 2: PERSONAL DETAILS

Age:

Address: _____

Immunisation status (measles): _____

Number/s and age/s of sibling/s:

“Does _____ attend childcare/preschool?”

Yes ☐ No ☐

If yes, where (name)?

SECTION 3: HEALTH INFORMATION

"How is he/she going"?

"How long was _____ unwell for after being discharged from hospital"?

"Did the doctor prescribe any medicine upon discharge"?

Yes ☐ No ☐

"If yes, what medicines"?

"Did he/she get better after taking the medicine"?

Yes ☐ No ☐ Unsure ☐

"Did _____ get any new symptoms after being discharged from hospital"?

Yes ☐ No ☐ Unsure ☐

"If yes, could you please describe the symptoms"?

"How long did these symptoms last for"? _____

"Did you take them to see a doctor or need to return to hospital following his/her ED visit"?

Yes ☐ No ☐ Unsure ☐

"If yes, which doctor/hospital"?

"Prior to his/her visit on 11th May, did you visit any other doctor's surgeries or hospital"?

Yes ☐ No ☐ Unsure ☐

"If yes, which doctor/hospital"?

SECTION 3: POTENTIAL EXPOSURE INFORMATION

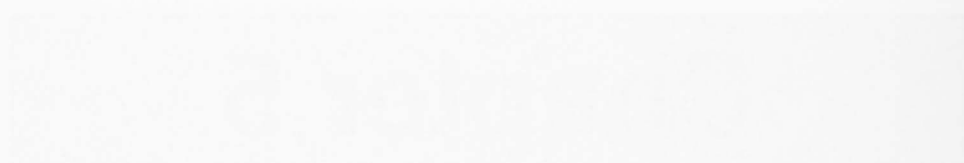
"How long you were in the hospital for on the 11th May?" _____

"How long did you wait in the ED waiting room?" _____

"Thanks for your time to day, would you mind if we contacted you in the future to clarifying anything else? Please do not hesitate to contact the infectious disease control team at the Parramatta public health unit on 9840 3603 if you have any further questions."

Chapter 5

Evaluation of the national Varicella Zoster Virus (VZV) notification system in Australia



Evaluation of the national Varicella Zoster Virus (VZV) notification system in Australia

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Abstract

Introduction

Primary varicella zoster infection (chickenpox) is a childhood disease that is generally mild. Shingles is the reactivation of dormant varicella zoster, most often occurring in the elderly. Both conditions may develop complications, leading to severe morbidity and mortality. In November 2005, universal varicella vaccination commenced in Australia for children 18 months of age, followed soon after by a catch-up program in children 10–13 years. In 2006, the Communicable Diseases Network of Australia (CDNA) recommended that chickenpox and shingles should be nationally notifiable through the National Notifiable Disease Surveillance System (NNDSS). By the end of 2008, all jurisdictions except NSW had adopted these recommendations. The aim of this evaluation was to determine whether the NNDSS for varicella zoster virus (NNDSSVZV) is achieving its objectives, primarily whether the NNDSSVZV is measuring the impact of the vaccine program.

Methods

Data were obtained from the NNDSS (2006–2012) for varicella zoster (chickenpox), varicella zoster (shingles) and varicella zoster (unspecified) and stakeholders were consulted. The system attributes were examined using evaluation frameworks for surveillance systems published by United States Centers for Disease Control (CDC) and Health Canada. The utility of the NNDSSVZV, and the sensitivity, predictive positive value, representativeness, data quality, stability, simplicity and flexibility were measured. The sensitivity and representativeness of the NNDSSVZV were assessed by comparison with the Bettering the Evaluation and Care of Health (BEACH) database, the Emergency Department Data Collection (EDDC) data from the NSW Ministry of Health and the Paediatric Active Enhanced Surveillance (PAEDS) network.

Results

The NNDSSVZV has a number of shortfalls which limits the utility of the system. It is unable to meet the objective of measuring the impact of the vaccine given that jurisdictions (except South Australia) began notifying disease after the implementation of the varicella vaccine program. The case definition for chickenpox and shingles is not being consistently applied among the jurisdictions, which affects the ability to interpret the data. Due to chickenpox being a generally mild illness, the sensitivity for individual notifications, overall is poor. As some jurisdictions only include laboratory notifications, the overall sensitivity is likely to be even lower. The sensitivity of the NNDSSVZV for

trends appears sufficient, when comparing the system to other data sources, although this varies by age group. Despite NSW not notifying chickenpox or shingles, the NNDSSVZV appears to be representative of disease patterns occurring in NSW emergency department presentations. One of the major strengths of NNDSSVZV is that it belongs to the NNDSS, a well-established surveillance system, and hence is stable, simple and potentially flexible. The data quality of the NNDSSVZV is high for notifications of chickenpox in patients less than seven years however could be further improved by conducting follow-up in all notifying jurisdictions. Data quality is not as good outside this age group. Among stakeholders, the acceptability of the system varies and the usefulness of system is a concern with suggestions that other surveillance systems may be more useful in meeting the objectives of varicella surveillance.

Conclusion

The NNDSSVZV in Australia does not appear to meet its objective of measuring the impact of universal varicella vaccine. Although notifications on chickenpox and shingles are captured by the current system, the large proportion of unspecified disease limits the utility of the system. The lack of resources among jurisdictions is a major barrier as follow-up cannot be conducted, therefore compromising the sensitivity and data quality of the NNDSSVZV. Review of the case definition and standardised reporting is recommended to ensure consistency among jurisdictions, which would improve the ability to interpret the data.

Abbreviations and Acronyms

| | |
|----------|--|
| ACT | Australian Capital Territory |
| AIHW | Australian Institute of Health and Welfare |
| APSU | Australian Paediatric Surveillance Unit |
| ASPREN | Australian Sentinel Practice Network |
| ATAGI | Australian Technical Advisory Group on Immunisation |
| BEACH | Bettering the Evaluation and Care of Health |
| CDC | Centers for Disease Control and Prevention |
| CDNA | Commonwealth Diseases Network of Australia |
| CSF | Cerebrospinal fluid |
| CVS | Congenital Varicella Syndrome |
| DAS | Data Acquisition System |
| ED | Emergency Department |
| EDDC | Emergency Department Data Collection |
| ELISA | Enzyme Linked Immune-Sorbent Assay |
| EIA | Enzyme Immunoassay |
| FAMA | Fluorescent Antibody to Membrane Antigen |
| FMRC | Family Medical Research Centre |
| GP | General Practitioner |
| HIV | Human Immunodeficiency Virus |
| ICD | International Classification of Diseases |
| IF | Immunofluorescence |
| Ig | Immunoglobulin |
| LabWISE | Virology and Serology Laboratory Reporting Scheme |
| MMRV | Measles, Mumps, Rubella and Varicella Vaccine |
| NCIRS | National Centre for Immunisation Research and Surveillance |
| NIP | National Immunisation Program |
| NNDSS | National Notifiable Diseases Surveillance System |
| NSW | New South Wales |
| NT | Northern Territory |
| NNDSSVZV | National Notifiable Disease Surveillance System for Varicella Zoster Virus |
| PAEDS | Paediatric Active Enhanced Disease Surveillance |
| PCR | Polymerase Chain Reaction |
| SMART | Specific, Measurable, Achievable, Realistic and Time-based |
| QLD | Queensland |

| | |
|-----|------------------------|
| SA | South Australia |
| TAS | Tasmania |
| US | United States |
| VZV | Varicella Zoster Virus |
| WA | Western Australia |
| ZIG | Zoster immunoglobulin |

Prologue

My role

I was responsible for reviewing the literature, formulating an evaluation plan and developing structured questionnaires for jurisdictional and Commonwealth stakeholders. I communicated with stakeholders to clarify responses to the questionnaire and requested enhanced data. I also liaised with researchers and stakeholders to obtain data from other sources. I analysed data from the National Notifiable Disease Surveillance System (NNDSS) and Paediatric Active Enhanced Disease Surveillance (PAEDS) and calculated rates obtained from the NSW Ministry of Health Emergency Department Data Collection (EDDC). I wrote a report on the evaluation, and with guidance from my supervisors developed suggested recommendations from the evaluation.

Lessons learned

I had always envisaged that the evaluation of a surveillance system component of the Master of Applied Epidemiology (MAE) program would be straight-forward and relatively quick. Unexpectedly, this project was perhaps the most challenging and time consuming of all my projects.

In hindsight, there were a number of things I would have done differently. However, despite the challenges and frustrations of this project, I have learnt so much from the evaluation.

Firstly, as with previous projects, I learnt the importance of formulating specific, measurable, achievable, realistic and time-based (SMART) objectives for the evaluation in addition to considering why this project was important. The project appeared large and the time to complete it short. Through direction and support from my supervisors, I learnt how to examine the available data sources systematically and how these sources could be useful in the context of the national surveillance system.

I learnt that every analysis and its interpretation in this chapter needed to be relevant to answering the objectives of the evaluation or enhancing the reader's understanding of varicella to justify its inclusion in the chapter. Being exposed to numerous data sources also allowed me to gain an understanding of the limitations of each data source.

I also learnt how to use SurveyMonkey® (<https://www.surveymonkey.com/>, online questionnaire software) which included developing an evaluation questionnaire and collecting and analysing the data.

An important lesson learned was the use of a framework to guide an evaluation. Sometimes however not all evaluations can easily be 'moulded' to a framework, thus I considered two frameworks during this evaluation.

I collaborated with many stakeholders during this project. This enabled me to improve my communication skills through discussions about the evaluation. Liaising with other researchers from the Family Medicine Research Centre (FMRC) and Paediatric Active Enhanced Disease Surveillance (PAEDS) to obtain their data improved my understanding of the nuances of the data from both sources.

Public health action

This evaluation has resulted in the formulation of numerous recommendations to assist the varicella surveillance system in meeting its objectives and improve the system's attributes. These recommendations will be forwarded to CDNA to consider and the report in the chapter will be sent to jurisdictional and Commonwealth stakeholders. A related manuscript will also be submitted to Communicable Diseases Intelligence for wider distribution to the public health community in Australia.

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There are numerous collaborators that were involved in this project who were generous with their time, knowledge and experience. The jurisdictional stakeholders who provided significant input through their responses including Mr David Coleman (Tasmania), Ms Lucinda Franklin (Victoria), Ms Emma Denehy (South Australia), Dr Anne Koehler (South Australia), Dr Angela Wakefield (Queensland), Dr Peter Markey (Northern Territory), Mr Gary Dowse (Western Australia) and Mr Alex Rosewell (New South Wales). I also acknowledge Nicolee Martin from the Department of Health and Ageing (DoHA) for her contribution to the evaluation and insight throughout the project.

Using additional data sources allowed me to collaborate with a number of public health researchers. I would like to thank Mr Chris Harrison (FMRC) and Ms Jocelynn McRae (PAEDS) for providing me with data and being so forthcoming in advice and support. Chris was responsible for analysing the BEACH data and calculating trends, as this was quite complicated analysis that needed to adjust for a number of confounders which was beyond the scope of the MAE and limited by time. I would also like to thank Ms Sophie Norton and Dr David Muscatello from New South Wales Ministry of Health for providing emergency department data for the evaluation.

A special thanks also to Dr Siobhan Reddel, Dr Hassan Vally and Mr James Fielding (all MAE alumni) who generously provided me with reports from their varicella-specific projects that they conducted during their MAE.

Introduction

Varicella zoster virus (VZV) is one of eight herpes viruses that belongs to the *Herpesviridae* family. Primary infection with VZV manifests as varicella (chickenpox). Herpes zoster (shingles) occurs following endogenous reactivation of VZV from its latent state in the sensory nerve ganglia of the dorsal root.¹

Clinical features

Chickenpox typically affects young children and presents with a generalised pruritic rash, mild headache, low-grade fever and malaise, the rash is commonly the first sign of disease in children.² In adults, a prodrome consisting of fever and malaise may precede the chickenpox rash by approximately 24–48 hours.² The lesions often appear in crops, initially on the head, and then on the trunk and later the extremities. Lesions evolve rapidly to papules, then vesicles, before erupting to form pustules which subsequently crust. Most crusts disappear within 20 days of the onset of prodrome.³

The most common complication in children <5 years is secondary bacterial infection and in adults ≥20 years is pneumonia.^{4, 5} Adults, immunocompromised individuals and neonates are particularly susceptible to complications. Varicella infection in pregnant women can result in intrauterine transmission to the foetus or neonate and lead to congenital varicella syndrome or neonatal varicella.⁶ Rare complications of chickenpox include encephalitis, aseptic meningitis and cerebellar ataxia.²

Shingles is more common in the elderly and can occur decades after primary infection with chickenpox.³ Disease generally presents as pain and parathesiae along the dermatome corresponding to where reactivation occurs, followed by vesicular eruption 2–3 days later. Vesicles are often unilateral and continue to form for approximately 3–5 days.⁷ Complications of shingles occurs in approximately 13–26% of patients, with the most common being postherpetic neuralgia; a painfully debilitating condition which greatly reduces the quality of life of those affected.^{8–10} Other complications include encephalitis, myelitis, cranial-nerve palsies and peripheral-nerve palsies.⁷

Pathogenesis

Chickenpox is highly contagious. The virus is transmitted through aerosol and droplets from the nasopharynx during the prodrome and from skin lesions for a period of 5–7 days after rash onset. The incubation period is 14–15 days (range 10–21 days)² and attack rates among susceptible household contacts have ranged from 61–100%.¹

Shingles occurs primarily due to a decline in cellular immunity to VZV. Risk factors include aging, immunosuppression or having chickenpox <12 months of age.¹⁰ Transmission of VZV from lesions via contact and airborne route can occur and lead to primary infection in susceptible individuals. Infectiousness begins one day prior to rash onset and remains until lesions have crusted over (usually five days), but may be prolonged in individuals with altered immunity.⁸

Diagnosis

Chickenpox is mainly diagnosed on clinical grounds; namely the characteristic vesicular rash. This diagnosis can be further supported by a history of recent exposure to a varicella (or herpes zoster) case.^{3, 11} Similarly, herpes zoster diagnosis is primarily through clinical diagnosis of characteristic skin eruptions accompanied by pain.³

When there is uncertainty of a diagnosis solely on clinical and epidemiological grounds, a laboratory diagnosis can be conducted, but depends on the availability of a clinical specimen (primarily skin lesions). Methods include: culturing the virus; identifying viral DNA through polymerase chain reaction (PCR); antigen detection by immunofluorescence (IF); and serology tests of Immunoglobulin (Ig)G, IgM and IgA antibodies through enzyme linked immune-sorbent assay (ELISA).¹²

Treatment and prevention

Symptomatic management is the mainstay for chickenpox and shingles treatment as a curative treatment for both conditions does not exist. In some instances acyclovir is recommended for chickenpox.¹³ In comparison, all patients with shingles are recommended antiviral treatment within 72 hours of rash onset.¹³

Prevention options following significant exposure to an infectious chickenpox or shingles case is limited to varicella vaccine or zoster immunoglobulin (ZIG), depending on the time since exposure. Varicella vaccine should be administered within five (preferably three) days of exposure to non-immune children and adults who have had significant exposure to chickenpox or shingles. ZIG should be given within 96 hours

(but some efficacy has been reported up to ten days) of exposure¹⁰ and is prepared from human plasma containing high VZV antibody titre. ZIG can prevent and attenuate disease among neonates, immunosuppressed children and pregnant women.¹⁴

The vaccine

In 1974, the first live attenuated monovalent vaccine (Oka strain) was developed¹⁵ and to date, is the only strain available (although genetic differences exists between vaccines).¹ Initially, one dose of vaccine was recommended in the United States (U.S.) in 1995. A two-dose schedule however was recommended following a number of varicella outbreaks,^{16–19} and of post-licensure trials which showed that vaccine effectiveness was significantly higher with two doses (98%) compared to one dose (94%).²⁰ Findings that the risk of breakthrough disease was higher in individuals administered only one-dose further supported the two-dose recommendation.²¹

The vaccine program in Australia

In Australia, two varicella monovalent vaccines have been registered for use in children since 1999 (Varilrix® and Varivax®).¹⁰ In 2003, the Australian Technical Advisory Group on Immunisation (ATAGI) recommended a single dose of vaccine for children 18 months of age and children 10–13 years of age with no history of vaccination or clinical disease.¹⁰ In November 2005, the national funding of one dose of vaccine for children 18 months of age commenced.¹⁰ The following year, a national catch-up program for children 10–13 years of age with no history of vaccination or clinical disease was introduced.²² Each jurisdiction decides the school grade(s) when vaccines are offered, guided by the national recommended age for vaccination.²³ Both the primary and catch-up dose continue to be funded under the National Immunisation Program (NIP).²⁴ Although a two-dose schedule is currently recommended in Australia, it is not funded under the NIP schedule.¹⁰ On 1 July 2013, a quadrivalent combination vaccine containing measles, mumps, rubella and varicella (MMRV) was added to the NIP for children aged 18 months.²⁵

The zoster (shingles) vaccine was licensed in Australia in 2006 and is recommended for use in adults aged 60–79 years.²⁶ There has however, been a shortage of this vaccine and it only recently became available in Australia.¹⁰ Given this, the effect of the vaccine using surveillance data could be estimated with pre- and post-vaccine surveillance data collected—an important impetus for the passive surveillance of shingles.

Passive surveillance of varicella zoster

Despite this incentive for the passive surveillance of varicella zoster, there has been much debate on whether to include VZV onto the notifiable disease list in Australia.^{27, 28}

A major impediment to the system is the difficulty in calculating the incidence of chickenpox given that only a small proportion of cases seek medical attention. In 2002 however, three years before the commencement of the varicella vaccination program, South Australia (SA) became the first jurisdiction to make VZV infection a notifiable disease.²⁸

Four years after being notifiable in SA, the Communicable Disease Network of Australia (CDNA) included varicella zoster (chickenpox), varicella zoster (shingles) and varicella zoster (unspecified) in the National Notifiable Disease List.²⁹ By the following year, all states and territories (except Victoria and New South Wales) included varicella zoster in their public health legislation as a notifiable disease following the recommendation by CDNA.³⁰ In 2008, Victoria adopted CDNA's recommendations and VZV became notifiable. Thus, 2009 was the first complete year where data were transferred to the National Notifiable Diseases Surveillance System (NNDSS) from all jurisdictions except New South Wales (NSW), the only jurisdiction in Australia where VZV continues not to be notifiable.²⁹

For the purposes of this evaluation, from this point forward, the passive surveillance system for VZV at a national level will be described as the National Notifiable Disease Surveillance System for Varicella Zoster Virus (NNDSSVZV).

Objectives of varicella surveillance

A joint National Immunisation Committee and CDNA Jurisdictional Executive Group committee was established in 2005 and given the task of managing the implementation of varicella surveillance. This encompassed establishing objectives of varicella surveillance which they formulated and included:ⁱ

- to measure the impact of universal varicella vaccine on the incidence of varicella infection in the Australian population;
- to measure the potential impact of the varicella vaccine program on the prevalence of varicella infection among specific populations such as unimmunised older children, adults and adolescents and Indigenous children and adults;
- to measure vaccine failure and provide data to measure vaccine effectiveness over time by age group; and
- to monitor possible changes in epidemiology of zoster infections in Australia as a result of the varicella vaccination program.

Alternative data sources

Given the infancy of the NNDSSVZV, other surveillance systems and data sources have been used to assess chickenpox and shingles epidemiology in Australia, mainly sentinel surveillance systems (**Appendix E1.1**).

Firstly, emergency departments (EDs) are used in some states and territories to monitor presentations due to chickenpox or shingles, particularly in NSW where VZV is not notifiable.^{14, 31, 32} For more serious cases requiring hospitalisation, the incidence and morbidity of VZV can be estimated using hospitalisation data.^{33, 34}

Secondly, the Virology and Serology Laboratory Reporting Scheme (LabVISE) has collected data since 1982. Laboratories around the country provide voluntarily reports on VZV which are collated and analysed quarterly.³⁵ Limitations exist however, as no information is collected that differentiates between chickenpox and shingles. Moreover, the uncertain validity and inconsistent reporting protocols of participating laboratories have been reported.³⁵

ⁱ CDNA varicella working group– internal discussion document

Thirdly, the Australian Sentinel Practice Network (ASPREN) is a network of general practitioners around Australia who report on a number of medical conditions, including chickenpox and shingles, on a weekly basis.³⁶ In a previous state-based evaluation of varicella surveillance in South Australia, it was recommended that collection of ASPREN data be terminated as it did not increase knowledge on the impact of varicella vaccine on VZV epidemiology.³⁷ Considering that little is known about the population presenting to sentinel GP sites, the data collected is of limited use, particularly for calculating the incidence of both conditions.³⁸

Additionally, active surveillance has been used to monitor severe infection in infants and children. Active surveillance of congenital varicella syndrome (CVS) and neonatal varicella has existed for many years through the Australia Paediatric Surveillance Unit (APSU).^{38, 39} Monthly report cards are sent to participating paediatricians and child health specialists to detect infant cases who match the case definition for the abovementioned conditions (**Appendix E5.1**).⁴⁰ The ongoing collection of reports at a national level has made APSU surveillance an important data source to monitor changes in CVS and neonatal varicella, particularly comparing pre- and post-vaccine periods.³⁸ The APSU, in collaboration with the National Centre for Immunisation Research and Surveillance (NCIRS) coordinates Paediatric Active Enhanced Disease Surveillance (PAEDS). PAEDS commenced in 2007 and consists of a network of five paediatric teaching hospitals across Australia who participate in reporting any child (1 month–15 years) who is hospitalised due to varicella.⁴¹

Public Health Importance

In Australia, the burden of chickenpox and shingles has been substantial. Prior to the availability of vaccine, it was estimated that 250,000 individuals (one birth cohort) would be infected with chickenpox each year.⁴² Chickenpox in Australia was generally seasonal, peaking during late winter, spring and early summer.⁴³ Severe disease was also observed with an average annual hospitalisation rate of 8.5 per 100,000 population. Nearly a quarter of these experienced complications; and between 1993 and 1997, there were 36 deaths reported.⁴⁴ Although chickenpox is known to be more severe in adults, hospitalisations were greatest in children 0–4 years; however, adults 60+ years experienced the longest median length of stay in hospital (seven days).⁴⁴

The significant burden of chickenpox can result in substantial economic and societal costs. It was estimated that in children <15 years of age, the direct cost of hospitalised cases of chickenpox was over 1.9 million Australian dollars per year. However, this did

not take into account the indirect and social costs of infections, such as a parent's time off work.⁴⁵ Given the significant costs of infection, a cost-effectiveness study in Australia found that the direct costs of a one-dose varicella vaccine program, particularly in infants was less than the direct costs of no vaccine program at all.⁴⁶

There has, however, been discussion on whether a one-or two-dose schedule should be funded. As previously mentioned, one-dose of varicella vaccine is free in Australia under the NIP. Due to the occurrence of breakthrough disease, which can be contagious and even lead to large outbreaks,⁴⁷ a two-dose schedule is recommended in Australia but currently not funded.¹⁰ An Australian study found that a funded two-dose schedule would reduce both the incidence of natural and breakthrough disease and thus lead to lower morbidity.⁴⁸ To inform policy on the funding of two-doses of varicella vaccine, further epidemiological evidence in Australia is still required, and hence it is important to monitor the burden of chickenpox at a national level.

The burden of disease of shingles has been reported to be even higher than chickenpox.³³ Prior to availability of varicella vaccine, there were approximately 150,000 new cases of shingles per year in Australia.³³ Seasonal patterns have not been observed in shingles.² Hospitalisations for shingles occurred most often in older adults (mean=68.6 years) and mean length of stay was 12.7 days. In July 1999 to June 2000 in hospitalised cases where shingles was the principal diagnosis, 51% of cases experienced complications and 22 deaths were recorded.³³ The severe morbidity of the disease has led to high healthcare costs. Between 2001 and 2005, the cost of shingles to Australia was estimated to be \$19–30 million.⁴⁹ In 1999 alone, around 59 200 of shingles cases were treated with antivirals in the community.³³

Following the availability of varicella vaccine, concern was raised of the change in shingles epidemiology following the availability of varicella vaccine. Hope-Simpson first postulated that exposure to wild varicella virus boosts the immune system, and without this exposure; may render an individual susceptible to shingles.⁵⁰ An Australia study using general practice data found that there had been a significant increase in the management of shingles between 1998 and 2009.⁵¹ In Victoria, hospitalisation rates due to herpes zoster appeared to increase between 1998 and 2007 (5% per year); however it was not clear what was behind the increase due to the ecological nature of the study.⁵² Given that shingles is most common in older age groups; the observed increase needs to be considered in the context of Australia's ageing population.⁵³

It is clear from what is outlined above, that chickenpox and shingles are of public health importance and need to be monitored, particularly in light of the introduction of universal varicella vaccine and the more recent availability of zoster vaccine. Given that it has been five years since the first complete year of Victorian data was submitted to the NNDSS, it is timely to evaluate the performance of the NNDSSVZV. Public health surveillance system evaluations are imperative to ensuring that health conditions of public health importance are being monitored efficiently and effectively.⁵⁴

Rationale for the evaluation of the NNDSSVZV

The aim of evaluating the NNDSSVZV was to highlight what (if any) improvements are required in monitoring VZV, specifically using varicella zoster notification data from jurisdictions. In light of the addition of the MMRV vaccine to the NIP in July 2013, the evaluation is timely and will inform the Australia Technical Advisory Group on Immunisation (ATAGI) Varicella Zoster Working Party and the CDNA Varicella Zoster Working Group. These groups will be considering surveillance of varicella in Australia in the context of the change from MMR and MMRV and also the possible public funding of zoster vaccine in the future.

Objectives of the evaluation of NNDSSVZV

- To ascertain how the NNDSSVZV is performing against the stated CDNA objectives of the passive surveillance of VZV;
- To examine the sensitivity of the NNDSSVZV in comparison with hospitalisation, PAEDS and Bettering Evaluation and Care of Health (BEACH) data;
- To assess the representativeness of the NNDSSVZV in comparison with NSW ED data;
- To determine the strengths and limitations of the current NNDSSVZV and consider any improvements required;
- To assess the usefulness of the NNDSSVZV, particularly the degree of public health action resulting from data collected by the NNDSSVZV; and
- To assess other attributes of the NNDSSVZV including data quality, acceptability, simplicity, stability and flexibility.

Methods

The following evaluation framework was adapted from frameworks for the evaluation of health surveillance systems published by the U.S. Centers for Disease Control and Prevention (CDC)⁵⁵ and Health Canada.⁵⁶

Stakeholder consultations

Two electronic self-administered jurisdictional and Commonwealth questionnaires were developed on SurveyMonkey® and included a subset of the jurisdictional survey for NSW (Appendix E2; E3; E4). In order to maximise response rates, stakeholders were followed-up with a telephone interview. One of the main purposes of consulting with stakeholders was to gain an understanding of the specific operation of the NNDSSVZV, particularly the notification process between jurisdictions and the Commonwealth.

Document review

To assess the operation of the NNDSSVZV and system components on a national level, NNDSS annual reports were reviewed to determine the operation of the system as a whole.

Data Analyses

NNDSS data

NNDSSVZV data for VZV (chickenpox), VZV (shingles) and VZV (unspecified) were obtained from the NNDSS database (2006–2012). SA notification data (2002–2005) for VZV were obtained from the SA Department of Health.

PAEDS data

Data were obtained from PAEDS on cases of hospitalisations due to varicella (2007–2012). Cases were patients from three tertiary paediatric hospitals in Victoria (Royal Children's Hospital), SA (Women's and Children's Hospital) and Western Australia (Princess Margaret Hospital). Year of diagnosis of varicella disease (chickenpox or shingles), date of birth, postcode and sex were used to examine whether cases were notified to the NNDSS; if the data of these variables were identical in both data sources, they were assumed to be the same individual. Whether a laboratory test was ordered for each case was also obtained from the investigators of the PAEDS study group.

Bettering Evaluation and Care of Health (BEACH) data

Data from the BEACH study (April 1998–March 2013) were obtained on encounters that were coded by the International Classification of Primary Care, version 2 as A72: Chickenpox and S70:Herpes Zoster.⁵¹ New encounters (i.e. the first time a patient sought medical care for the problem managed) were collected as well as all total encounters (new and old problems managed). The number of varicella zoster tests (culture and serology) was collected. Additionally, number of PCR tests ordered was obtained for encounters where chickenpox and herpes zoster were managed.

NSW Emergency Department Data Collection (EDDC) data

As VZV infections are not notifiable in NSW, ED presentations of chickenpox and herpes zoster (1998–2012) based on International Classification of Diseases (ICD)-10-AM/ICD-10 codes B01 and B02 by age group were obtained from the NSW Ministry of Health (1998–2012). Data were collected from 45 NSW EDs that consistently reported to the Emergency Department Data Collection (EDDC) during this period.

The type and timing of data used for each jurisdiction are summarised in Table 1.

Table 1. Data sources compared by year and jurisdiction, 1998–2012

| Jurisdiction | NNDSSVZV Notifications | PAEDS ^a | BEACH [*] | ED data |
|--------------|---------------------------|--------------------|--------------------|-----------|
| NSW | - | - | 1998-2012 | 1998-2012 |
| VIC | 2009-2012 | 2009-2012 | 1998-2012 | - |
| QLD | 2006-2012 | - | 1998-2012 | - |
| SA | 2002-2012 | 2007-2012 | 1998-2012 | - |
| WA | 2006-2012 | 2007-2012 | 1998-2012 | - |
| NT | 2006-2012 | - | 1998-2012 | - |
| ACT | 2006-2012 | - | 1998-2012 | - |
| TAS | 2006-2012 | - | 1998-2012 | - |

^aBEACH year was from April to March

^{*}QLD joined the PAEDS network in July 2012 and was not included in data analysis

Surveillance System Utility and Attributes

Utility

The utility of a system is the measure of the system's contribution in preventing and controlling an adverse health-related event. Its utility may also be in identifying the importance of an adverse health-related event which previously was not recognised as important and or through its contribution to performance measures.⁵⁵

The utility of the NNDSSVZV was measured by how well it performed against its objectives and the public health action that occurred as a result of the NNDSSVZV. Firstly, notification rates from the NNDSSVZV were calculated to determine if the impact of the varicella vaccine program could be measured for chickenpox and shingles in the Australian population and also among specific populations. Secondly, NNDSSVZV data were reviewed to determine whether vaccine effectiveness could be measured over time. Additionally, VZV (unspecified) notification rates by age group were calculated to assist in conjecturing whether these notifications were chickenpox or shingles, based on the known epidemiology of both diseases. Stakeholders were also consulted to determine whether they thought the objectives of the NNDSSVZV were being met and what public health action had occurred because of the system.

The following system attributes were selected on the basis of their relevance to the objectives of the NNDSSVZV: sensitivity; data quality; representativeness; acceptability; stability; flexibility; and positive predictive value.

Sensitivity

The sensitivity of a surveillance system refers to the proportion of cases of a health event detected by the surveillance system and the system's ability to detect outbreaks.⁵⁵ With no known estimates of the number of chickenpox cases that occur in the post-vaccine era, a denominator data does not exist to calculate the sensitivity of the NNDSSVZV. A proxy of the measurement of sensitivity of the surveillance system was obtained through calculating the proportion of laboratory tests that were requested for chickenpox and shingles managed in the BEACH dataset.

Firstly, rates of ED presentations for chickenpox and shingles per 100 000 population in NSW by age group were compared to NNDSSVZV rates.

Secondly, chickenpox and shingles notification rates from all jurisdictions and at a national level (excluding NSW) were compared to SA notification rates. SA was considered the 'gold standard' as notifications commenced in 2002.

Thirdly, chickenpox notifications rates by age group (<1 year; 1–4 years; 5–9; 10–19 years; 20–39 years; and 40+ years) were compared to rates of chickenpox and shingles managed from the BEACH study and NSW EDDC dataset. Prior to comparing NNDSSVZV annual rates with BEACH annual rates, seasonality of disease notifications were assessed to see if comparison of BEACH year (April to March) with calendar year may impact on the results.

Additionally, to further determine the ability of the NNDSSVZV to capture severe disease, notification rate were compared to national hospitalisation rates for chickenpox from an unpublished manuscript.⁵⁷ Lastly, severe cases of chickenpox and shingles in children < 15 years old from the PAEDS dataset were obtained to determine whether cases in the PAEDS system were captured by passive surveillance and used as an index of sensitivity of severe infection with chickenpox. Chi squared tests were used to determine whether a significant difference in proportion of PAEDS cases with a positive test result were notified compared to cases with no test result.

Data Quality

Data quality refers to the completeness and validity of the data in the system.⁵⁶ To assess the data quality of the NNDSSVZV, completeness of the following fields were assessed: demographic data including vaccination status, onset date of symptoms and Indigenous status.

Representativeness

The representativeness of the system is the ability of it to accurately describe the occurrence of disease over time and its distribution by place and person.⁵⁵ To measure the representativeness of the NNDSSVZV, rates of ED presentations for chickenpox and shingles per 100 000 population in NSW by age group were compared to NNDSSVZV rates.

Acceptability

The willingness of persons and organisations to participate in the surveillance system is imperative to the accuracy, consistency and completeness of data.⁵⁵ Acceptability

was primarily determined through stakeholder consultations. However, a measure of acceptability was also conducted through the calculation of the proportion of the number of VZV unspecified cases over the total number of VZV (chickenpox and shingles) cases. In some jurisdictions, clinicians are requested to provide clinical information to health authorities following a laboratory notification. Anecdotally, it is widely accepted that majority of notifications come from laboratories. It was assumed that all notifications would result in efforts by health authorities to contact the clinician. And if a case was unspecified, clinicians did not respond to requests by the health authority.

Simplicity

Simplicity is defined as the ease of operation and structure of a surveillance system.⁵⁵ The simplicity of the NNDSSVZV was determined through stakeholder consultations and includes responses on the operation of the system and review of NNDSS annual reports. The simplicity of the CDNA case definitions for VZV infection were also reviewed.

Stability

The stability of a system is its reliability and availability.⁵⁵ To determine the stability of the system, relevant stakeholders were consulted.

Flexibility

The flexibility of the system is its ability to adapt to changing information needs or operational procedures with limited additional time, human resources or funds.⁵⁵ The flexibility of the NNDSSVZV was measured through stakeholder consultations.

Positive predictive value

The positive predictive value (PPV) refers to the proportion of reported cases that actually have the health-related event under surveillance.⁵⁵ Case definitions for varicella disease were reviewed to consider whether there is a possibility of false positives occurring. The proportion of probable cases over total cases (by year) was calculated from NNDSSVZV data to determine whether testing for VZV had increased over time for all jurisdictions (except NSW). Lastly, NNDSSVZV cases were examined by the laboratory method used to diagnose disease, in the context of the sensitivity and specificity of the laboratory methods used.

Results

A total of nine stakeholder were consulted, and included jurisdictional and Commonwealth stakeholders.

Operation and System Components

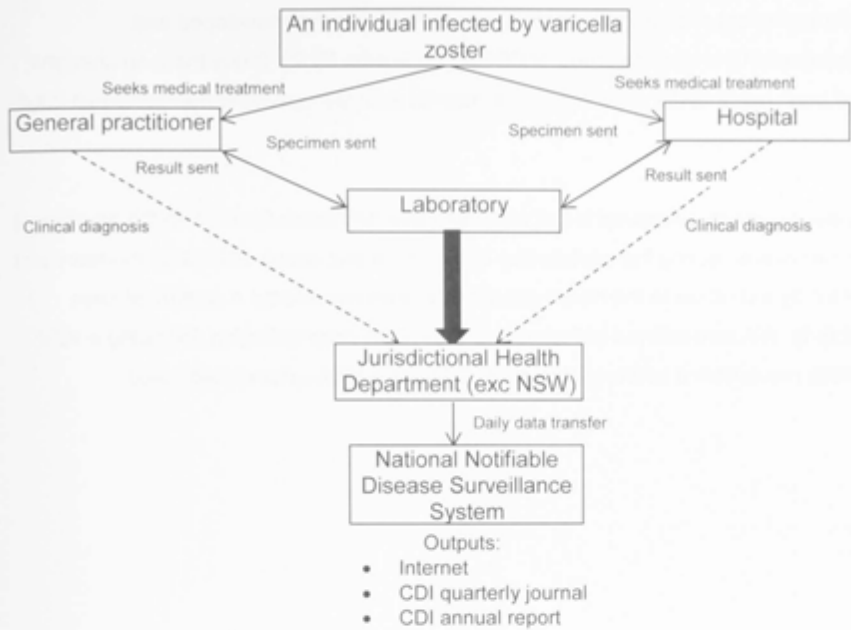
Legislation

Under the provision of public health jurisdiction in states and territories, notifications of varicella zoster (chickenpox), varicella zoster (shingles) and varicella zoster (unspecified) are electronically forwarded to the DoHA on a daily basis. Prior to September 2007, there was no legislative requirement for jurisdictions to forward notifications to the Commonwealth.⁵⁸ However, from September 2007, the National Health Security Act 2007 received royal assent, providing a legislative basis to authorise the exchange of health information between the Commonwealth and jurisdictions. De-identified data on a nationally agreed list of communicable diseases are voluntarily forwarded to the Commonwealth for the purposes of surveillance of communicable diseases at a national level. As part of the core dataset of the NNDSS, mandatory data fields include: a unique record reference number; the notifying jurisdiction; disease code; confirmation status; and the date of notification to jurisdictional health authorities.⁵⁹

Data flow

The structure and flow of data of VZV notifications through the NNDSS is displayed in Figure 1. Data transfer occurs through the Data Acquisition System (DAS) on a daily basis, and data are automatically transferred into the Microsoft Access NNDSS database.⁵⁸ Notifications requiring updates can occur at any time and quality control measures are in place through data constraints to monitor the validity of data.

Figure 1. Flow chart of the varicella zoster virus notification system



All notifications reported from Tasmania and the Australian Capital Territory (ACT) were from laboratories (**Table 2**). In the ACT, notifications were sent to ACT Health by laboratories. If the clinical notes section of the form had 'query shingles' or 'query chickenpox', cases were classified as varicella zoster (shingles) or varicella zoster (chickenpox), respectively. In Tasmania, laboratory notifications were forwarded to the health department who subsequently sent out a form via fax to the clinician to collect clinical information on the case. This is similar in the Northern Territory (NT) where a questionnaire is sent to clinicians to record clinical and demographic information following a laboratory notification. Although Queensland health authorities can receive notifications from laboratory and clinicians, almost all notifications were from laboratories. In Victoria, Western Australia (WA), SA and the NT, both clinical and laboratory notifications occur.

In 2006, a national notifiable case definition for varicella zoster (chickenpox), varicella zoster (shingles) and varicella zoster (unspecified) was first developed and implemented by a working group of CDNA (**Appendix E1.2**). Since then, no changes have been made to the case definitions despite a review occurring during August 2008.

60

In most instances, jurisdictions follow CDNA case definitions for VZV. In SA however, it was discovered during the stakeholder consultation that cases without a laboratory test notified by a clinician to the health department were considered a confirmed case (**Table 2**). WA also differed in their use of the CDNA case definition, including a VZV positive result from a cerebrospinal fluid (CSF) as a VZV (unspecified) case.

Table 2. Case definitions, reporters and degree of follow-up of varicella notifications by jurisdictions

| Jurisdiction | CDNA case definition | Notified by Lab | Notified by clinician | Follow-up |
|--------------|---|-----------------|-----------------------|---|
| NSW | - | - | - | - |
| VIC | ✓ | ✓ | ✓ | No follow-up conducted, however, if chickenpox notifications occur in a closed setting, an outbreak investigation will be conducted and cases are contacted. |
| QLD | ✓ | ✓ | | Chickenpox notifications in children <8 years old. Follow-up of 10% of a sample of chickenpox also occurs periodically. Follow-up is through clinician interview. |
| SA | ✓ But defines cases with 'clinical evidence' only as confirmed cases | ✓ | ✓ | Case-by-case basis and risk assessment conducted to determine whether follow-up should occur. Case and clinician interviews are conducted if follow-up occurs. |
| WA | ✓ Accepts VZV positive cerebrospinal fluid specimens as VZV (unspecified). | ✓ | ✓ | Follow-up of children 0–5 years occurs, healthcare and childcare workers and asylum seekers. Case and clinician interviews are conducted. |
| NT | ✓ | ✓ | ✓ | All chickenpox notifications are followed up by faxing the clinicians following a laboratory notification to obtain clinical information, particular to verify vaccination status of notifications. |
| TAS | ✓ | ✓ | | Case-by-case basis, usually follow-up is the provision of advice to individual clinicians with no direct public health action conducted in the majority of notifications. |
| ACT | ✓ | ✓ | | Case-by-case basis, in some instances follow-up with clinician to recommend specific public health action (for example the administration of ZIG). |

The degree of follow-up of cases varied among notifying jurisdictions. Some jurisdictions conducted follow-up through case and clinician interviews. However, in most cases, notifications were reviewed on a case-by-case basis to determine whether public health follow-up should be conducted.

In the NT, all cases were followed up. Clinicians were contacted following a laboratory notifications with a focus on identifying high-risk contacts. The level of risk in contacts was also examined in clinician notifications. The aim of the follow-up of high-risk contacts was to implement preventative measures. Similarly in SA, risk assessments were conducted to identify high-risk contacts. In SA, clinicians were encouraged to conduct follow-up and enforce control and preventative measures themselves. In WA, follow-up was prioritised depending on age and other identified risk factors. In contrast, Queensland focused on following-up notifications in children under eight years of age and also periodically follow-up 10% of all notifications. Prior to 2010, attempts were made to follow-up all VZV in Queensland however with limited resources and capacity poor completeness occurred.

Tasmania and the ACT follow-up on a case-by-case basis. In Tasmania, this occurred through the provision of information and advice to clinicians who were responsible for the follow-up of cases and the implementation of preventative measures with assistance in public health measures, available on request. Victoria reported not conducting any routine follow-up, however in the past had investigated an outbreak that occurred in a closed setting.⁶¹ Similarly, if a notification occurred in a healthcare worker or childcare worker, follow-up was reported to occur.

Surveillance System Utility and Attributes

Utility

Overall, the NNDSSVZV is not performing well against its objectives; and little public health action has occurred as a result of the surveillance system.

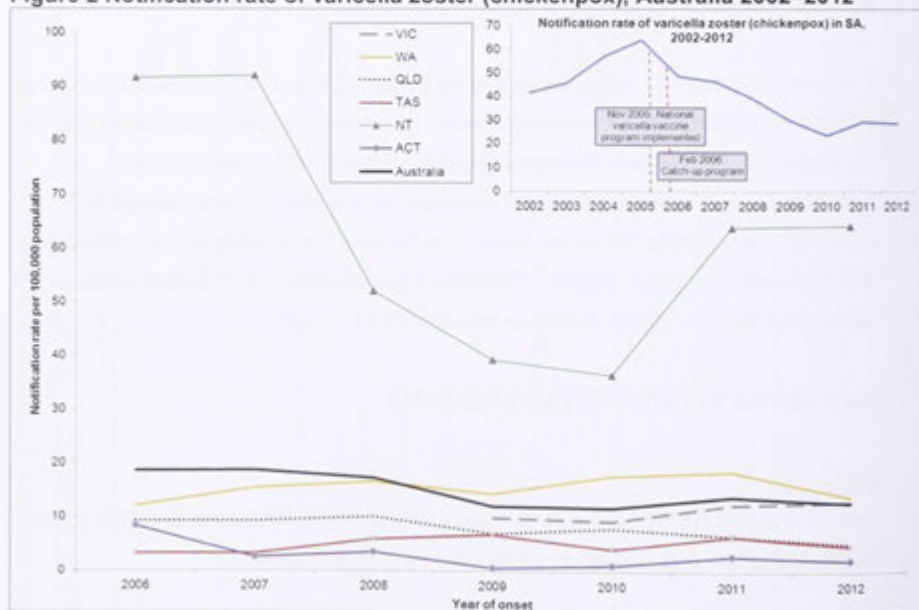
Performance of the system against its objectives

Objective 1: To measure the impact of universal varicella vaccine on the incidence of varicella infection in the Australian population

NNDSS data

The utility of the NNDSSVZV to measure the impact of the varicella vaccine on the incidence of disease is generally weak as varicella only became notifiable in six of the seven notifying jurisdictions after the implementation of the vaccine program. Therefore, at a national level, notification rates pre- and post-vaccine cannot be calculated using the NNDSSVZV data. On a jurisdictional basis, only SA data can be used to measure vaccine impact as they began notifying VZV in 2002 and it is worthwhile noting that since 2005, a decline in notification rate of chickenpox in SA has occurred, suggesting that the varicella vaccine may have led to a reduction in disease (Figure 2).

Figure 2 Notification rate of varicella zoster (chickenpox), Australia 2002–2012^{*,^†}



* Since 2002, VZV infection became notifiable in South Australia

[^] Victorian data available 2009–2012, all other jurisdictions data available from 2006 except NSW where VZV is not notifiable

[†] Includes confirmed and probable cases

Stakeholder consultations

From the stakeholder consultations (notifying jurisdictions and the Commonwealth), six of the eight respondents believed that the current NNDSSVZV was measuring the incidence of varicella infection in the Australian population whilst two were neutral.

One jurisdictional stakeholder however, commented:

While I have ticked 'agree' it doesn't mean the notification data are either accurate or complete or that the measures are fool proof. A range of data needs to be considered, not just that of the NNDSS.

Given the infancy of the NNDSSVZV, more time may be required to improve its usefulness. Indeed, the increase in the rate of chickenpox in the NT (**Figure 2**) was acknowledged by one stakeholder who suggested that the increase may be due to the increased testing of cases rather than an increase in disease. It was mentioned that clinicians may have previously been unaware of diagnostic tests for chickenpox (for example PCR) however; more recently have become more aware of these tests which has resulted in an increase in testing.

The first calendar year that data from all notifying jurisdictions were received occurred in 2009. One jurisdictional stakeholder commented:

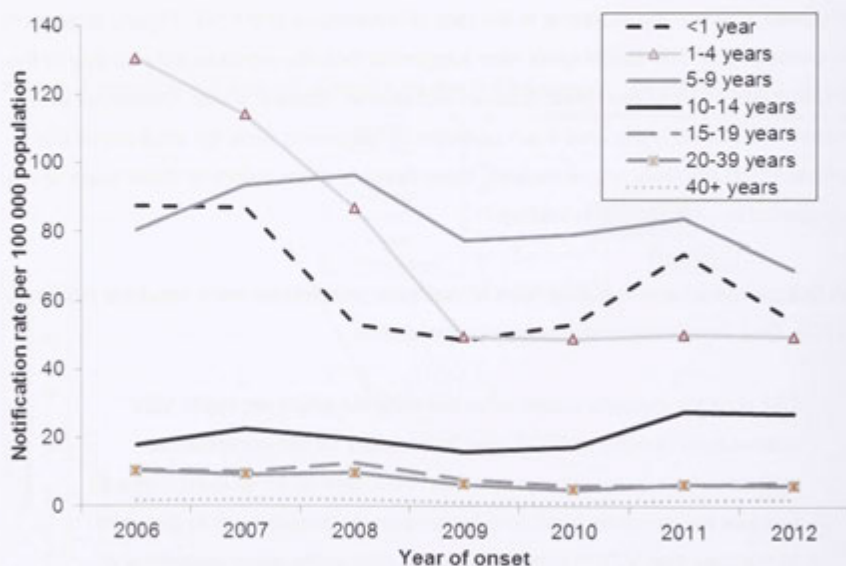
Our plan for varicella zoster virus surveillance when we made VZV notifiable at the end of 2008, was to basically let the surveillance system run as a passive system (with no follow-up for at least 5 years), to allow for clinicians (and, to a lesser extent, laboratories) to get used to the idea that VZV is notifiable, let the data settle into a pattern, and then to evaluate what the data looked like...

Objective 2: To measure the potential impact of the varicella vaccine program on the prevalence of varicella infection among specific populations such as unimmunised older children, adults and adolescents and Indigenous children and adults

NNDSS data

Objective 2 is dependent on the completeness and validity of specific variables that will be discussed in more detail under the system attribute 'data quality'. Notification rates by age-group are shown (**Figure 3**). These were highest in children < 1 year, 1–4 years and 5–9 years. In the 1–4 year age group, notification rates appeared to be decreasing until 2009 when it plateaued. Universal vaccine is recommended at 18 months, suggesting that this reduction may be due to more children in the 1–4 year age group having been vaccinated against varicella and thus leading to a reduction in susceptible individuals in this age group and subsequently a decline in cases of chickenpox. Again the significance of this in the context of the vaccine program is impossible to state at this stage.

Figure 3 Notification rate of varicella zoster (chickenpox) by age group, 2006–2012^{*^}



* 45 chickenpox notifications excluded due to missing age

[^] Victorian data available 2009–2012, all other jurisdictions data available from 2006 except NSW where VZV is not notifiable

+ Includes confirmed and probable cases

Stakeholder consultation

Five of the eight respondents (notifying jurisdictions and the Commonwealth) agreed or strongly agreed that the incidence of varicella infection was being measured in unimmunised children and Indigenous children, whilst two respondents were neutral and one disagreed. In unimmunised adults and Indigenous adults, three agreed that

the incidence of varicella infection was being measured by the NNDSSVZV, three were neutral and two disagreed.

Given that adult cases were not followed-up in most jurisdictions, one stakeholder felt that the incidence of adult cases would not be captured well and that the jurisdictions that do follow-up adults had small populations and due to this would not be representative at a national level.

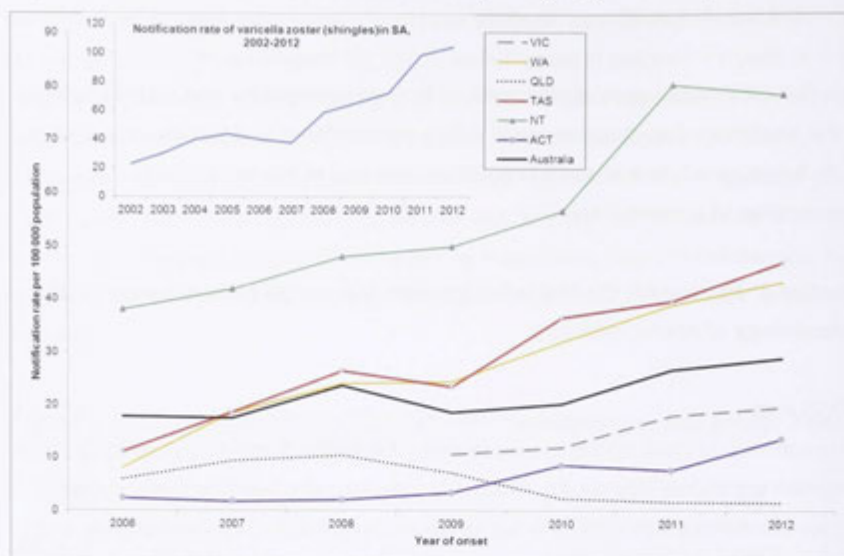
Objective 3: To monitor the impact of the varicella vaccination program on the epidemiology of zoster infection

NNDSS data

The occurrence of zoster is being measured by the NNDSS and overall rates by jurisdiction are shown (**Figure 4**). Nationally, rates show a slight increase, however whether this reflects a true effect or an artefact is impossible to determine given that the disease only became notifiable after the vaccine program started. As for chickenpox, South Australian notification data could potentially be used to monitor the vaccine impact; interestingly these rates have been increasing over time – whether this indicates a true increase (due to decreased circulating virus and subsequently decreased immunity due to natural boosting) or an artefact due to increased reporting is unclear (**Figure 4**). Notification rates by age-group are shown (**Figure 5**). These were highest in adults ≥ 75 years and in the three oldest age groups (45–59; 60–74; 75+ years). In these age groups, notification rates appeared to be increasing with a peak in notifications observed in 2008 – again the significance of this in the context of the vaccine program is impossible to state at this stage.

Of importance however, is that with the recent availability of a herpes zoster vaccine in Australia, pre-vaccine notification data on shingles will be useful in determining if the vaccine has impacted on the burden of shingles at a national level.

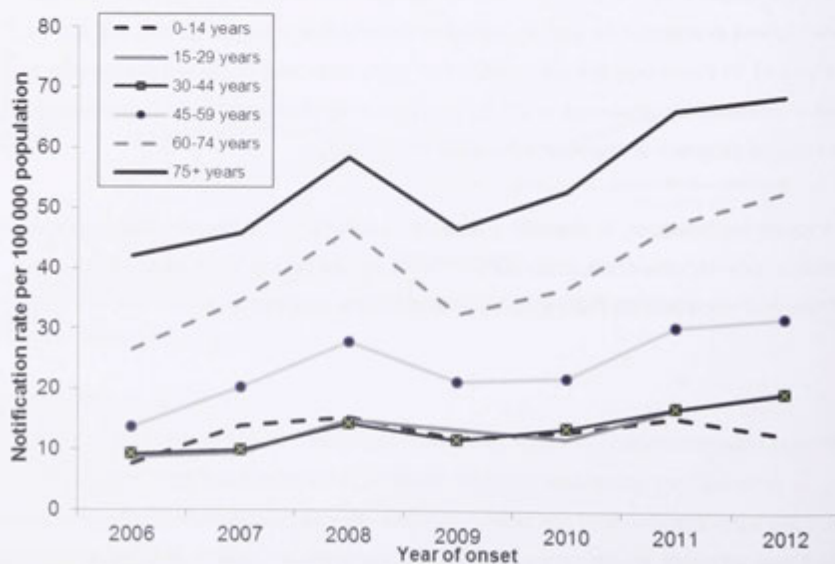
Figure 4 Notification rate of varicella zoster (shingles), Australia, 2002–2012^{*^}



^{*} Since 2002, VZV infection became notifiable in South Australia

[^] Victorian data available 2009–2012, all other jurisdictions data available from 2006 except NSW where VZV is not notifiable

Figure 5 National notification rate of varicella zoster (shingles) by age group, Australia, 2006–2012



^{*} 56 shingles notifications excluded due to missing age

Stakeholder consultation

Among the jurisdictional stakeholders which notify varicella infection and the Commonwealth, seven of the eight respondents agreed that the NNDSSVZV is monitoring the changes in the epidemiology of shingles in Australia.

Objective 4: To measure vaccine failure and provide data to measure vaccine effectiveness over time by age group

Another objective of the NNDSSVZV was to measure vaccine effectiveness over time by age group. This is dependent on the quality of the data on vaccination status which will be discussed in more detail later. However, from stakeholder consultations, under the Vaccine Preventable Diseases Surveillance Project Agreement, jurisdictions are encouraged to achieve at least 95% in completeness of the vaccination status data field in chickenpox cases aged < 7 years.

Of the notifying jurisdictional and Commonwealth stakeholders, five of the eight respondents agreed or strongly agreed that this objective was being met by the current system.

Additional objectives

Two additional objective of the surveillance system that a jurisdictional stakeholder identified was:

To identify/monitor outbreaks (for example in settings such as child-care) and to assess morbidity, at least crudely based on hospitalisation data to the extent recorded in notifications.

However they were unsure as to whether the current surveillance system in place was able to meet this objective. Additionally, it was identified that not all jurisdictions collect information on hospitalisations, hence it would be difficult to examine morbidity on this, particularly if the completeness of this field was poor.

Overall, there was no over-riding agreement that the notification system was meeting its objectives. In relation to the national notification system, one jurisdictional stakeholder remarked:

Many of the objectives of varicella surveillance are being met through alternative systems.

The users of notification data

Stakeholder consultation

Stakeholders believed that the main users of national notification data were jurisdictional and Commonwealth surveillance officers and researchers. However, one stakeholder commented that although they assumed there were multiple users of the NNDSSVZV it didn't necessarily mean that the NNDSSVZV was helpful.

Public health action

Stakeholder consultation

An important measure of the usefulness of a surveillance system is whether any public health action or changes in public health policy occurs. Stakeholders from three jurisdictions reported that the only use for varicella notifications in their jurisdiction was the production of routine reports. Five of the respondents were unsure whether the NNDSSVZV led to any public health action at a national level, and the remaining three believed no public health action had occurred. Similarly, six of the eight respondents were unsure whether the NNDSSVZV had led to changes in public health policy at a national level; one believed that it had led to changes, whilst another believed no public health policy changes had occurred. Despite this, a number of stakeholders felt that as the NNDSSVZV becomes more established, future policy changes are likely.

I'm not aware that policy has changed as yet based on the varicella zoster notification data per se, but presumably it may do as time goes by, depending on what the data reveal and in concert with data from other sources (hospitalisation data, overseas studies, etc.)

Early days yet ...but ongoing prioritised follow-up of certain cases may prompt policy changes – we'll see...

Of the notifying jurisdictional stakeholders, three of the seven respondents were aware that NNDSSVZV data were used to generate national reports, whilst three were unsure and one respondent believed no reports were generated.

The usefulness of a surveillance system is also determined by the following system attributes: sensitivity, data quality, representativeness and acceptability. This will be discussed in more detail below.

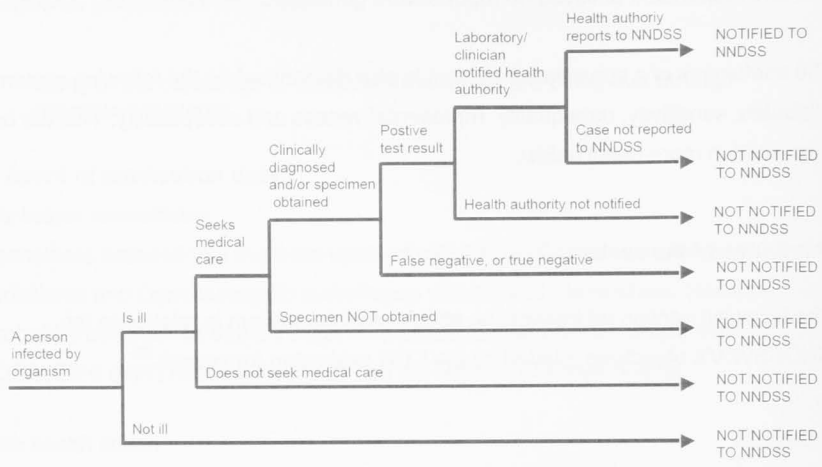
Attributes of the system

The following section addresses the attributes of the system in relation to the NNDSSVZV's objectives, guided by the CDC evaluation framework.⁵⁵

Sensitivity

The sensitivity of the NNDSSVZV is likely to be poor for a number of reasons. Figure 6 demonstrates the notification process to the NNDSS for all notifiable diseases and shows the high proportion of cases not notified to the NNDSS. Specific attributes of varicella decrease the likelihood of sensitivity. Given that mild disease is generally experienced by most cases, only a small proportion may seek medical care. Additionally, several jurisdictions collect all, or the vast majority of their notifications from laboratories, further reducing the sensitivity of a system that is assumed to capture only a small proportion of disease occurring in the community.

Figure 6. Notifiable fraction of communicable diseases



Source: NNDSS Annual Report 2010

The poor sensitivity of the NNDSSVZV is demonstrated by the low proportions of laboratory tests that were requested for chickenpox and shingles managed in the BEACH dataset (Table 3). This suggests that in a community setting, the majority of cases of chickenpox and shingles are clinically diagnosed and thus not notified to the NNDSSVZV. The proportion of test requests however, appeared to be increasing, indicating that sensitivity may be increasing over time. Between 2000 and 2012, there were no PCR tests for chickenpox encounters and eight PCR test requests for shingles encounters in the BEACH dataset. Given that the main laboratory method used to diagnose chickenpox and shingles is PCR in the NNDSS (discussed in more detail below under positive predictive value), demonstrates the poor sensitivity of the NNDSSVZV at capturing individual notifications in the community.

Table 3. Number (weighted) and proportion of GP-patient encounters at which chickenpox and shingles was managed as a new problem where a confirmatory laboratory test (serology or culture or PCR) was ordered.*

| | Year | | | | | | | | | | | | |
|---|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| | 2000 | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 |
| Total number of tests ordered | 6.2 | 14.4 | 34.0 | 24.5 | 29.8 | 31.9 | 38.9 | 26.3 | 55.3 | 75.2 | 63.2 | 69.4 | 49.7 |
| Total new encounters of chickenpox and shingles | 231.3 | 174.7 | 191.5 | 206.2 | 199.4 | 176.6 | 180.4 | 208.6 | 159.6 | 149.0 | 139.4 | 143.1 | 151.4 |
| Proportion of encounters with test request (%) | 2.7 | 8.2 | 17.7 | 11.9 | 15.0 | 18.0 | 21.6 | 12.6 | 34.7 | 50.5 | 45.3 | 48.5 | 32.8 |

* Numbers are not whole numbers as weighting occurred

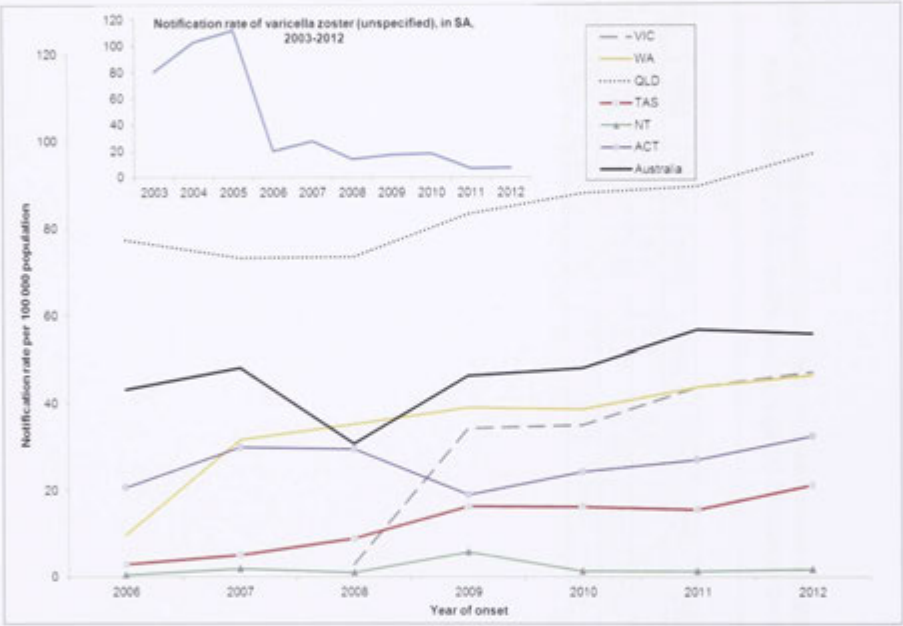
Moreover, the proportion of tests by year was consistently highest in the 5–59 year age group; which indicates the uncertainty among clinicians in diagnosing varicella zoster in this age group (**Table 4**). It does suggest that in the 0–4 year and 60+ year age groups, few tests are being requested and the proportion of test requests have been sporadic with no real pattern observed (although it appears to be increasing in the 0–4 year age group). Given this fluctuation in the BEACH data, it is possible that the sensitivity in notifications is also changing.

Table 4. Proportion (%) of GP-patient encounters at which chickenpox and shingles was managed as a new problem where a serology or culture or PCR test was ordered by age group, 2000–2012, BEACH data

| Age group | Year | | | | | | | | | | | | |
|------------|------|------|------|------|------|------|------|------|------|------|------|------|------|
| | 2000 | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 |
| 0–4 years | 0.0 | 0.0 | 2.5 | 0.9 | 1.9 | 0.0 | 13.5 | 0.0 | 9.8 | 6.4 | 15.6 | 45.5 | 14.2 |
| 5–59 years | 5.1 | 12.5 | 29.0 | 22.0 | 27.4 | 29.3 | 34.1 | 20.7 | 51.2 | 91.0 | 72.1 | 82.0 | 72.3 |
| 60+ years | 0.0 | 0.0 | 0.0 | 0.0 | 1.1 | 4.3 | 3.2 | 1.2 | 17.5 | 1.9 | 14.4 | 8.7 | 2.8 |

Furthermore, without clinical information on positive laboratory results of varicella zoster, a large proportion of tests were not classified as chickenpox or shingles which further contributed to the lower sensitivities of both diseases. Unspecified varicella disease does not provide information on the epidemiology of disease. However, calculating the rates of notifications by jurisdiction and age group still provided valuable insight on the performance of the NNDSSVZV Nationally, a slight increase in VZV (unspecified) notifications was observed which may suggest that the sensitivity of the NNDSSVZV for each disease is decreasing (Figure 7).

Figure 7 Notification rate of varicella zoster (unspecified), Australia, 2003–2012[^]

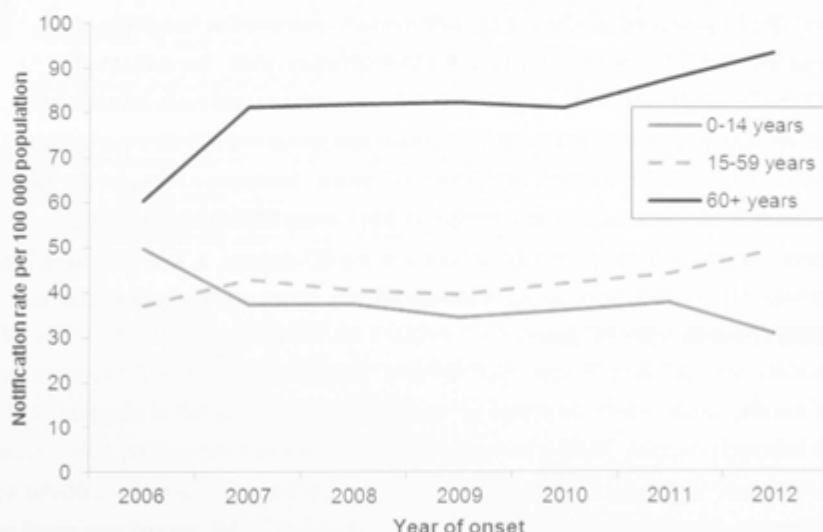


* Since 2002, VZV infection became notifiable in South Australia, unspecified VZV data available since 2003

[^] Victorian data available 2009–2012, all other jurisdictions data available from 2006 except NSW where VZV is not notifiable

When stratifying by age, notification rates were highest in adults ≥ 60 years and increased over time (**Figure 8**). In contrast, VZV (unspecified) notification rates in children 0–14 years of age appeared to be decreasing. The trends in notification rates by age group differed, which might be due to a change in follow-up over time. The reduction observed in children 0–14 years may have occurred due to increased follow-up of notifications in children < 7 years as part of the Vaccine Preventable Diseases Surveillance Project Agreement. If this was the case, it would suggest that the sensitivity of the system was increasing over time. In adults aged ≥ 60 years however, an increase in notification rate of unspecified disease may suggest that the sensitivity of the NNDSSVZV for this age group was decreasing based on the increase in rate over time. If these rates were indeed a true depiction of disease, based on our understanding of VZV, it would be likely that unspecified disease in 0–14 years were chickenpox and ≥ 60 years were shingles notifications. If this was the case, the unspecified disease trends were similar to the national trends that were observed for chickenpox (**Figure 2**) and shingles (**Figure 4**) suggesting that although there were a high number of VZV unspecified notifications, the sensitivity of the system in capturing trends for chickenpox and shingles is occurring.

Figure 8 Notification rate of varicella zoster (unspecified), Australia by age group, 2006–2012*



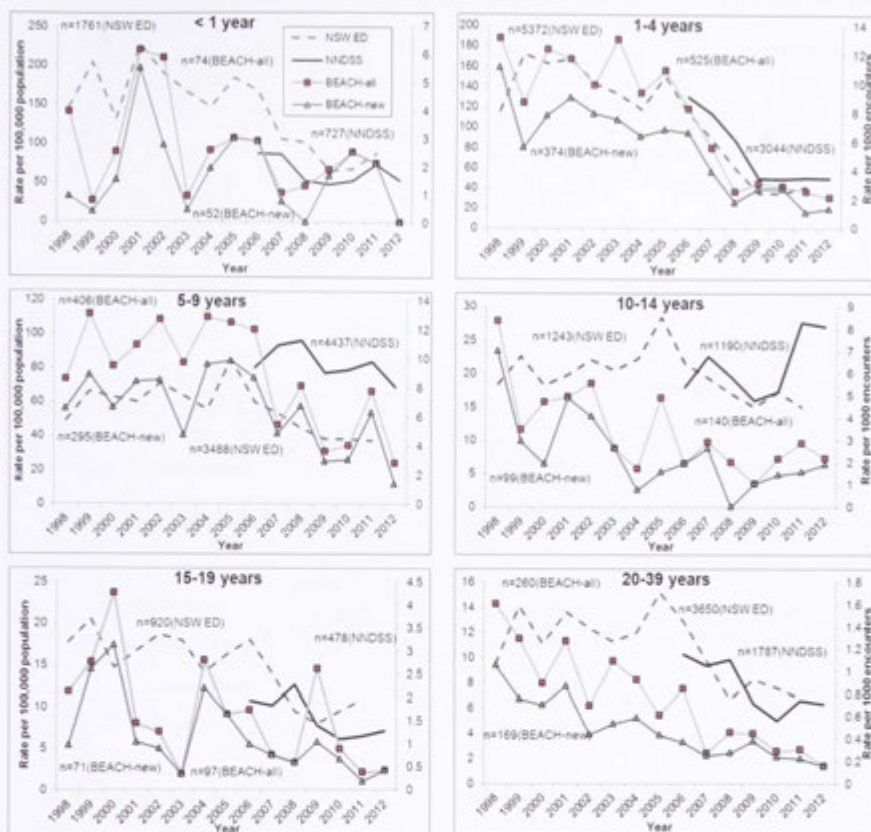
* 9 unspecified notifications excluded due to missing age

Further evidence of the poor sensitivity of the NNDSSVZV existed when comparing it to NSW ED data. Despite only collecting ED data from 45 hospitals in NSW and using the entire NSW population to calculate disease rates, the rates were comparable to NNDSS notification rates, nationally (**Figures 15 and 16**). As ED presentations would capture more severe disease, it would be expected that the sensitivity of the ED surveillance system would be lower than the NNDSS. Although these rates may be interpreted as NSW having a higher burden of disease for chickenpox and shingles, it suggests that the sensitivity of the NNDSS for chickenpox and shingles is extremely poor.

Of more importance is the consistency in the reporting of disease in the NNDSSVZV, to allow the true pattern of disease to be captured. The sensitivity of the NNDSSVZV in capturing disease patterns was better in some age groups compared to other age groups.

In specific age groups, patterns of notification rates for chickenpox were similar to rates of chickenpox managed in GPs, indicating that the NNDSSVZV was sensitive enough to capture the pattern of disease that is occurring in the community (**Figure 9**). This was most evident in the 1–4 year age group, where patterns of disease from the three data sources corresponded closely to each other. In the older age groups (10–14 years; 15–19 years and 20–39 years), patterns were observed to be similar when comparing BEACH (new encounters) rates to notification rates. The pattern of NNDSSVZV notification rates and BEACH (all encounters) rates were also similar in the older age groups; except for the 15–19 year age group in 2009 where a peak occurred in the BEACH dataset. In children 5–9 years, divergence between the three sources existed. Peaks occurred in 2008 and 2011 in the BEACH and NNDSS datasets; however, these peaks did not occur in the ED dataset. A four-year increase in chickenpox presentations occurred in the GP setting, which was not reflected in the NNDSSVZV or in NSW ED data.

Figure 9. A comparison of rates of disease of chickenpox by age group from multiple data sources, 1998–2012^{*,^}



* Since 2002, VZV infection became notifiable in South Australia

[^] Victorian data available 2009–2012, all other jurisdictions data available from 2006 except NSW where VZV is not notifiable

#BEACH year is between March to April

20–44 years age group used for NSW ED rates in the 20–39 year age group graph

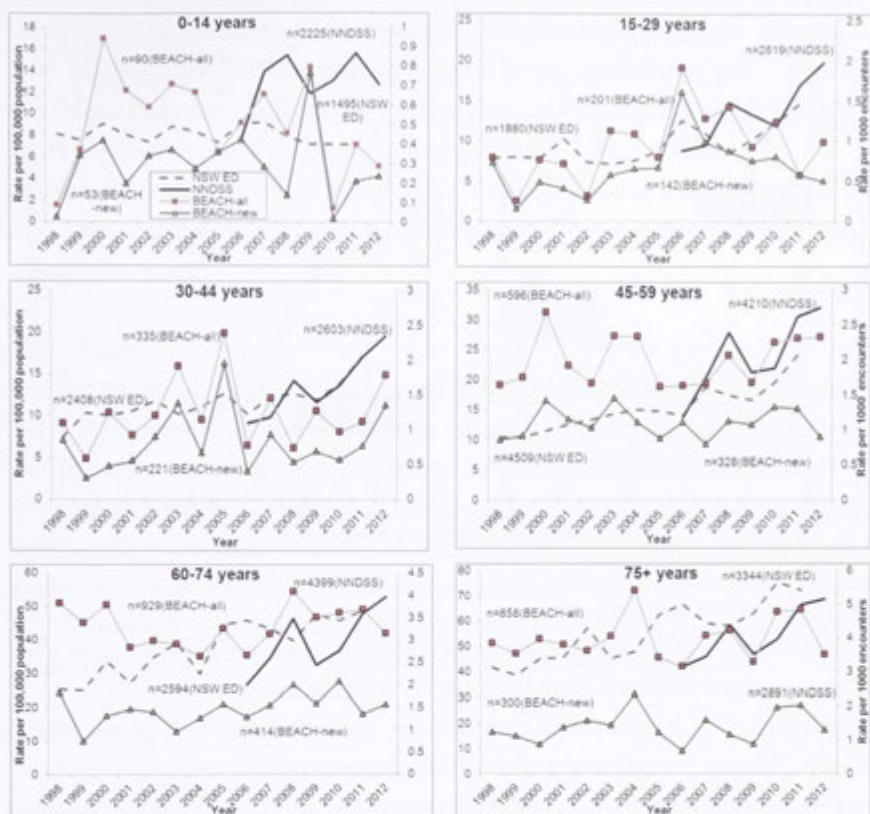
n= total number of cases in data source during time period that data was collected

The sensitivity of the NNDSSVZV for shingles in capturing pattern of disease varied by age group, in comparison with BEACH and NSW ED data (Figure 10). The notification rate of shingles in the younger age groups (0–14 years and 15–29 years) differed by data source, particularly between notification data and BEACH data. It suggested that the NNDSSVZV was not sensitive in capturing the burden of shingles in the community for these age groups. BEACH data in the younger age groups fluctuated substantially whilst NSW ED data appeared to be more stable. Similar patterns of disease in the older age groups (30–44 years; 45–59 years; 60–74 years; 75+ years) occurred. It

suggested that the NNDSSVZV for shingles was sensitive in capturing disease patterns in older age groups but not the younger age groups.



Figure 10. A comparison of rates of disease of shingles by age group from multiple data sources, 1998–2012^a#



* Since 2002, VZV infection became notifiable in South Australia

^a Victorian data available 2009–2012, all other jurisdictions data available from 2006 except NSW where VZV is not notifiable

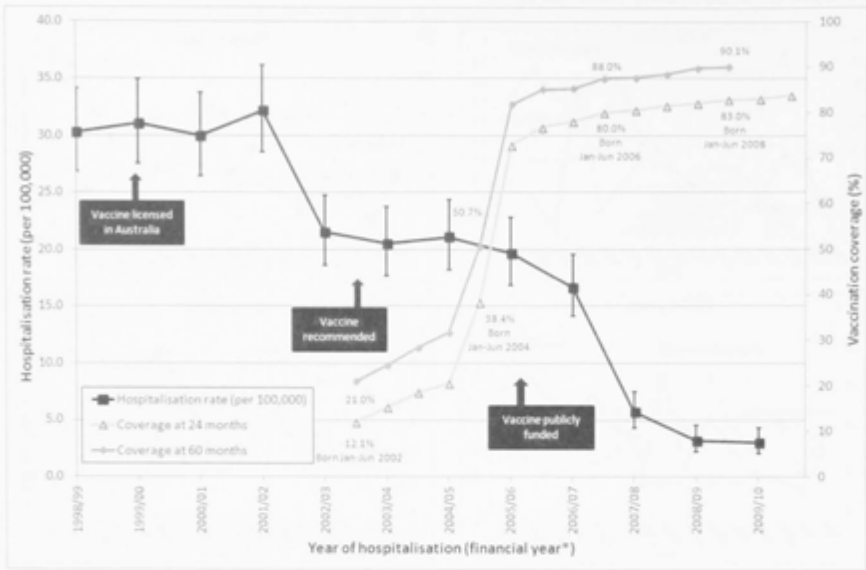
#BEACH year is between March to April

45–54 year age group and 65–74 year age group used for NSW ED rates for 45–59 year age group and 60–74 year age group graphs, respectively

n= total number of cases in data source during time period that data was collected

Another data source that has been used to examine the impact of vaccine in Australia has been hospitalisation data. Since 2001/2002, a reduction in rate occurred, with the greatest reduction observed after the implementation of the vaccine program (**Figure 11**). A slight decline of NNDSS VZV chickenpox rates was observed from 2006 (**Figure 2**) which was consistent with the pattern of hospitalisation rates during the same time period suggesting that the NNDSSVZV was sensitive in capturing the burden of severe disease for chickenpox.

Figure 11. Hospitalisation rate of chickenpox in Australia, 1998–2010⁵⁷



PAEDS cases and notifications

The sensitivity of the NNDSSVZV was poor in capturing severe disease in infants and children. Between 2007 and 2012, a total of 111 varicella hospitalisations (96 chickenpox and 15 shingles) were reported in SA, WA and Victoria through the PAEDS network (**Table 5**). A notification to the NNDSS occurred in 54% (n=52) of PAEDS chickenpox cases and 73% (n=11) PAEDS shingles cases. Among PAEDS chickenpox cases, 80% (47/59) of cases with a positive test result were notified to the NNDSS compared to 14% (5/47) of cases with no test result ($\chi^2=40.1$, $p<0.001$). Additionally, 89% (8/9) PAEDS shingles cases with a positive test result were notified to the NNDSS compared to 50% (3/6) of cases with no test result (Fisher's exact=0.24).

Table 5. Number and proportion of PAEDS cases notified to the NNDSS 2007–2012 from Victoria, South Australia and Western Australia*

| Disease | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | Total |
|------------|-----------|-----------|-----------|----------|-----------|----------|-------|
| | n(%) | n(%) | n(%) | n(%) | n(%) | n(%) | n |
| Chickenpox | 3 (75.0) | 10 (62.5) | 11 (61.1) | 7 (33.3) | 13 (61.9) | 8 (50.0) | 96 |
| Shingles | 2 (100.0) | 1 (100.0) | 3 (100.0) | 2 (66.7) | - | 3 (50.0) | 15 |

* 2009–2012 PAEDS cases from Victoria included

Stakeholder consultation

During the stakeholder consultations, a number of jurisdictions raised concerns of an idiosyncrasy of the CDNA case definition, which may lower its sensitivity. In Western Australia, positive PCR tests for varicella zoster from a cerebrospinal fluid (CSF) specimen without lesions are notified. Under the CDNA case definitions (**Appendix E1.2**) these cases would not be considered a probable or confirmed case of chickenpox, shingles or unspecified disease. Although these WA cases did not meet the CDNA case definition, they were notified to the NNDSS as varicella zoster (unspecified) cases.

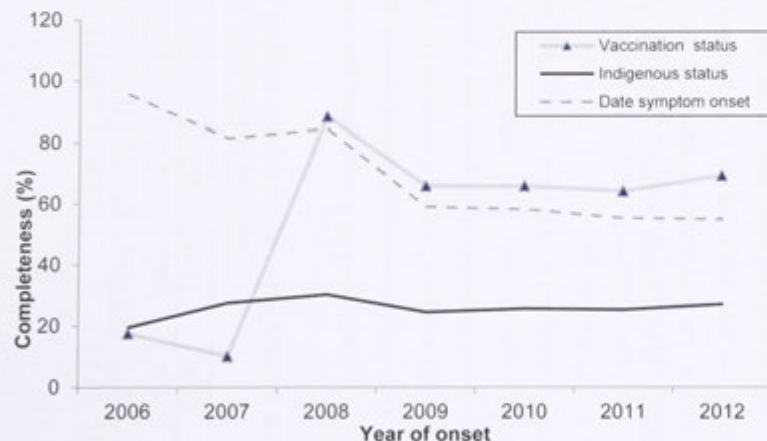
Data Quality

Overall, the data quality of chickenpox and shingles notifications in the NNDDSVZV is high but poor for unspecified disease. The key issue hindering the data quality of varicella surveillance was the high proportion of all VZV notifications that were unspecified (**Table 6**). Consequently, a large proportion of VZV notifications cannot be interpreted; not only because it was not known whether a notification was chickenpox or shingles, but also due to the low completeness of demographic information (**Figure 12**). Moreover, the proportion of unspecified disease as a total of all varicella zoster notifications did not change, indicating that data quality was not improving.

Table 6. Number and proportion of notifications by disease and year, 2006–2012

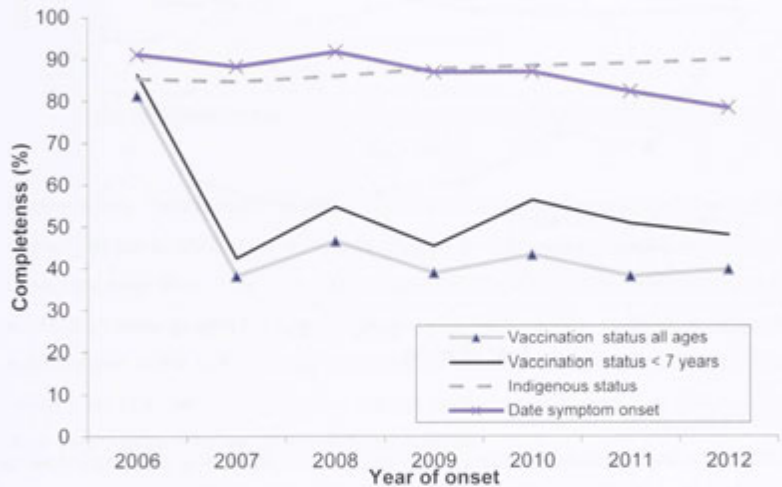
| Disease | Year | | | | | | | | | | | | | | | |
|-------------|-------|------|-------|------|-------|------|-------|------|-------|------|-------|------|-------|------|--------|------|
| | 2006 | | 2007 | | 2008 | | 2009 | | 2010 | | 2011 | | 2012 | | Total | |
| | N | % | n | % | N | % | n | % | n | % | n | % | n | % | n | % |
| chickenpox | 1,621 | 24.7 | 1,667 | 22.2 | 1,566 | 19.6 | 1,755 | 15.6 | 1,748 | 14.7 | 2,092 | 15.2 | 1,953 | 13.1 | 12,402 | 16.8 |
| shingles | 1,178 | 18.0 | 1,560 | 20.8 | 2,148 | 26.9 | 2,721 | 24.2 | 2,993 | 25.2 | 3,999 | 29.0 | 4,405 | 29.6 | 19,004 | 25.7 |
| unspecified | 3,764 | 57.4 | 4,284 | 57.0 | 4,261 | 53.4 | 6,785 | 60.3 | 7,147 | 60.1 | 7,720 | 55.9 | 8,524 | 57.3 | 42,485 | 57.5 |

Figure 12. Data completeness of varicella zoster (unspecified) notifications, 2006–2012



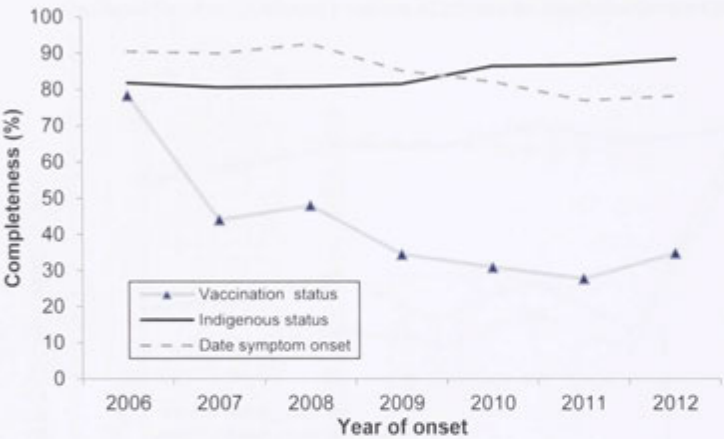
However, for notifications which were coded as chickenpox and shingles, data quality was good, particularly for onset date of symptoms and Indigenous status. It is important to note, that completeness was found to vary by age for vaccination status. The completeness of Indigenous status was high for chickenpox notifications (**Figure 13**). Similarly, completeness of the field date of onset was high, however, appeared to be declining over time. For vaccination status for NNDSSVZV chickenpox notifications, completeness was higher in children < 7 years compared to all ages.

Figure 13. Data completeness of varicella zoster (chickenpox) notifications, 2006–2012



For NNDSSVZV shingles cases, the completeness of data fields Indigenous status and onset date of symptoms were high. Completeness over time increased slightly for Indigenous status and decreased for onset date of symptoms (**Figure 14**). The completeness of vaccination status was much lower; completeness was highest in 2006 however since then declined.

Figure 14. Data completeness of varicella zoster (chickenpox) notifications, 2006–2012



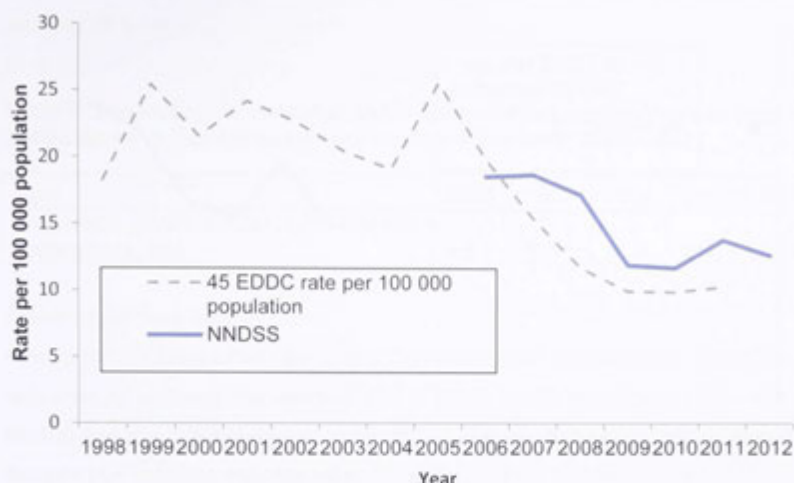
Stakeholder consultation

Although SA has a well-established passive surveillance in place and actively follow-up notifications, between 2006 and 2012, the vaccine status field was 25% complete in the state. It is understood that a data extraction issue exists with SA notifications in the NNDSSVZV that might be influencing the completeness of vaccination status. At a national level, this is of concern as it reduces the validity of the data and hence makes it difficult to interpret the results of any analysis. Further, the extent of this issue is not known.

Representativeness

The pattern of NNDSSVZV rates for chickenpox with rates in chickenpox presentations from NSW EDs was similar, suggesting that disease rates captured in the NNDSSVZV reflected what was occurring at a national level (**Figure 15**).

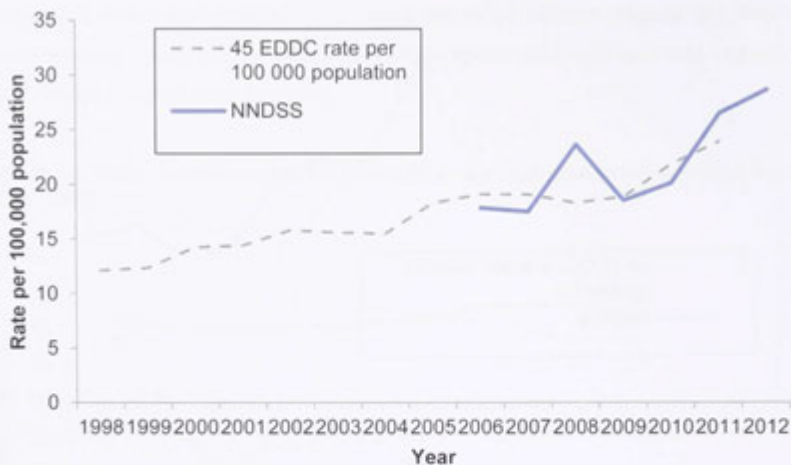
Figure 15. Comparison in rate of shingles notifications versus NSW emergency department presentations, 1998–2012



Furthermore, comparison between notification rates for shingles and rate of shingles presentations in NSW EDs over time shared a similar pattern, with an increase observed over time. It indicated that the NNDSSVZV represented what was occurring nationally, despite NSW not notifying disease (**Figure 16**). In 2008, a peak of shingles notifications in the NNDSSVZV occurred which was not reflected in NSW ED data. Apart from this particular year, the similar patterns suggested that NNDSS shingles data was representative of the national picture.

Representativeness is also related to data quality and system operations (including reporting mechanisms). Inconsistent case definitions and reporting by jurisdictions to the Commonwealth have been discussed in detail above; however can additionally compromise the representativeness of a surveillance system.

Figure 16. Comparison in rate of shingles notifications versus NSW emergency department presentations, 1998–2012



Stakeholder consultations

From jurisdictional stakeholders, the main limiting factor communicated was the poor representativeness of surveillance data given NSW does not notify and the second most populous state Victoria does not routinely follow-up cases. It was noted however, that the intensity of follow-up by jurisdictions was limited by the resources available to them.

Despite stakeholder concerns of the representative of the NNDSSVZV, from the comparisons between NSW ED and NNDSS data, NNDSS data appeared to provide a representative picture of what was occurring at a national level, including in NSW.

Acceptability

The acceptability of the NNDSSVZV was generally good, however there were a number of issues identified that could increase the acceptability of the system.

Following a laboratory notification of chickenpox or shingles, clinicians receive a fax from health authorities (NT and Tasmania) requesting clinical details to determine whether the notification was chickenpox or shingles. The low proportion of unspecified VZV infections suggests that acceptability in these two jurisdictions was high (Table 7). However, appeared to decline based on the increased proportion of unspecified disease over time. It is important to mention that in the NT, health authorities will ring the clinician to return the form if they had not responded by 4–7 days. In Tasmania; no

resources were available to chase up forms not sent back. The number of unspecified disease thus would depend on how actively jurisdictions follow-up clinicians after sending off a fax

Table 6. Proportion of varicella zoster (unspecified) notifications of total varicella notifications in Tasmania and the Northern Territory, 2006–2012

| Year | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 |
|---|------|------|------|------|------|------|------|
| Proportion of VZV unspecified/ VZV total notifications) [%] | 4.2 | 6.6 | 10.5 | 21.0 | 16.8 | 12.6 | 15.7 |

Stakeholder consultations

Among the notifying jurisdictional and Commonwealth stakeholders, five of the eight respondents believed that varicella was of public health importance whilst one was neutral and one felt that it was unimportant. Similarly, five of the eight stakeholders thought that notifying varicella was a good use of their time whilst the remainder were unsure. One respondent commented:

I think the importance lies in the future. Notification and the vaccination program have probably not been in place for long enough as yet for the data collected to be readily interpretable.

Whilst another commented:

There could be other ways of doing this surveillance.

One stakeholder stated that there was a

Lower public health priority for mild form of disease.

Five of the eight notifying jurisdictional and Commonwealth stakeholders believed that the current requirements for chickenpox reporting nationally were adequate however some believed that completeness of data needed to be improved with suggestions to focus on vaccination status in children ≤ 5 years.

One stakeholder also commented

Data completeness and quality probably needs to be improved.
Important to evaluate the system as it currently operates.

To improve the acceptability of the NNDSSVZV, jurisdictional stakeholders suggested that: more national consistency was required; a series of national guidelines for varicella should be developed; better reporting methods were needed (particularly for clinicians (e.g. online reporting)) and; a focus on clinician notifications was required in the NNDSSVZV.

Simplicity

Stakeholder consultations

One of the major strengths of VZV surveillance was that it is part of the well-established NNDSS which is connected to all states and territories (although NSW does not notify VZV disease). Six of the seven notifying jurisdictional stakeholders felt that reporting VZV notifications to the NNDSS was easy and that the flow of information to and from the NNDSS was adequate. In a previous evaluation of the NNDSS, the structure of the NNDSSVZV was deemed simple however, it was noted that it had taken some time to develop a national standardised database.⁵⁸

The CDNA case definitions were not simple to administer based on the lack of consistency in applying the case definitions by the jurisdictions. The interpretation of NNDSSVZV data at a national level is thus difficult. Whilst some jurisdictions accept all cases as confirmed, others require laboratory evidence and the degree of follow-up varies which leads to variations in the level of completeness of data fields. A resounding sentiment among stakeholders was the limited resources available with which compromised their ability to follow-up cases.

Stability

Stakeholder consultations

Another major strength of the NNDSSVZV was how stable the system is, being part of a well-established and stable surveillance system infrastructure. Data transfer, back-up, storage and the release of data are considered to be stable. Unscheduled outages do not occur. Having existed from many years, the NNDSS is maintained regularly and runs efficiently. Reports are prepared every quarter and annual reports are also developed that include VZV notification data.

Flexibility

The flexibility of NNDSSVZV is particularly important. However, it is not known how flexible the NNDSSVZV will be until a major change occurs. Following the introduction of universal varicella vaccine, the incidence of chickenpox is expected to decline and become rarer. It is possible that in the future, the objectives of the NNDSSVZV will expand to include the detection of chickenpox outbreaks. It was concluded by stakeholders that the NNDSSVZV had the potential to be able to detect outbreaks however it would be challenging to start genotyping specimens and collecting additional information. Moreover, the NNDSSVZV would need to be flexible in conducting vaccine failure analysis in outbreaks. Improvements would need to be made in collecting vaccination status for this to occur.

Positive predictive value

Although varicella zoster (chickenpox) and varicella zoster (shingles) are predominantly clinically diagnosed,⁶² a number of laboratory tests exist to confirm cases of chickenpox and shingles as part of the CDNA case definition.⁶³ These include detection of virus antigen by direct immunofluorescence (IF), viral isolation through cell culture, detection of viral nucleic acid by PCR or detection of virus-specific antibodies using serology (Appendix E6.1).⁶⁴⁻⁶⁶

The most commonly used laboratory methods to test for varicella zoster in the NNDSS was PCR. Detection of viral nucleic acid by PCR can occur rapidly and is the most sensitive of all diagnostic tests for varicella zoster (~100%) but can be affected by the number of copies of target. The specificity of the test is dependent on the primer/probe design. The PPV is high in symptomatic individuals however in asymptomatic or immunosuppressed individuals, may be reduced due to low or no viral load. For varicella zoster (shingles), sensitive is higher if the specimen is an older lesion.⁶⁷ Based on the assumption that most cases would be symptomatic when seeking medical attention, the PPV is likely to be high.

Of the 12,402 chickenpox notifications between 2006 and 2012, 43.7% of notifications had a PCR conducted. However, no laboratory diagnosis methods were used in 55.2% chickenpox notifications. For shingles notifications, 66.2% of the 19,004 notifications had a PCR test conducted whilst no laboratory diagnosis method was used in 33.0% of notifications. Given that PCR was the most used test coupled with the requirement of clinical evidence, and in some cases, an epidemiological link to a laboratory confirmed case; the PPV of a confirmed case was high.

The PPV of a clinical diagnosis chickenpox (probable case) is unknown; however, the existence of a characteristic vesicular rash suggests that it would be high. Other conditions that may be considered during differential diagnosis include allergic skin reactions, herpes simplex infection, herpes zoster infection and enteroviruses³ suggesting that without laboratory diagnosis, or an epidemiological link to a case, there is a possibility of false positives from a clinical diagnosis. There is a possibility though that misdiagnosis may occur, particularly if modified disease occurs in a vaccinated individual. Moreover, there is a possibility that as disease becomes rarer due to the introduction of universal vaccination, clinicians may become unfamiliar with the disease and clinical diagnosis may not be valid. The proportion of probable cases of chickenpox in the NNDSSVZV decreased over time (Table 7). Although this is unlikely to be of a concern as chickenpox is still a common disease, it may be of concern in the future when chickenpox becomes rarer.

The PPV from a clinical diagnosis of herpes zoster is also assumed to be high. In a primary healthcare setting in the Netherlands, the PPV was found to be 91%; (95% CI: 87%–94%).⁶⁸ This suggests that the probable cases of shingles from the NNDSSVZV were likely to be true cases of shingles. As with chickenpox, the proportion of probable cases in shingles notifications increased over time which suggests that testing has decreased (Table 7).

Table 7.Proportion (%) of probable cases by disease, 2006–2012, NNDSS

| Disease | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | Total |
|---------------|------|------|------|------|------|------|------|-------|
| Chickenpox | 15.9 | 18.8 | 16.4 | 36.4 | 35.1 | 34.9 | 35.1 | 28.2 |
| Shingles | 4.2 | 4.6 | 6.2 | 14.0 | 12.7 | 11.9 | 12.7 | 10.8 |
| Unspecified | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.1 | 0.0 |
| Total disease | 4.7 | 5.1 | 4.9 | 9.1 | 8.4 | 8.7 | 8.4 | 7.5 |

Discussion

Strengths of the NNDSSVZV

The main strength of the NNDSSVZV is that it forms part of Australia's well established and well performing national notifiable diseases surveillance system. Overall, attempts are being made for the NNDSSVZV to achieve its objectives, specifically through providing jurisdictions financial incentives to collect the vaccine status of at least 95% in children under seven years. Increasing completeness of vaccinations status would allow a more valid measurement of vaccine failure. Vaccination status data were better for children under seven years (although 95% target was not reached) than all ages; however, this may be due to an issue with data extraction between jurisdictions and the Commonwealth which needs further investigation.

The NNDSSVZV was simple, stable and appeared representative. It is not a sensitive system, but was sensitive in capturing disease patterns at a national level in certain age groups (i.e. younger age groups for chickenpox and older age groups for shingles) when compared to long-standing data sources. The NNDSSVZV was useful in producing output based on reports published quarterly in the CDI and in the NNDSS annual report.

Limitations of the system

The NNDSSVZV had a number of limitations which need to be considered when interpreting the data. Firstly, notification data could not assess the impact of the varicella vaccine as the disease only became notifiable in most jurisdictions after the implementation of the vaccine program.

Although the sensitivity of the NNDSSVZV was poor, the system does not aim to capture all disease in the community and hence is not an important attribute. Rather, it was more important that the NNDSSVZV's sensitivity remained constant so that trends in disease notifications were interpreted appropriately. The sensitivity of the NNDSSVZV; however, varied due to the inconsistency in reporting mechanisms among jurisdictions. Some jurisdictions only collected laboratory notifications; others also collected notifications from clinicians. Follow-up differed by jurisdiction and the case definition agreed to by CDNA was not being consistently implemented in all notifying jurisdictions. Lower sensitivity would occur in jurisdictions only notifying through laboratories. Moreover, it was difficult to understand the national picture of disease when some jurisdictions defined a clinical diagnosis of disease as a confirmed case

whilst others include cases that, under the national case definition, were not defined as a case of chickenpox or shingles. Any changes to the methods by which a jurisdiction reported notifications over the time period analysed would also make rates difficult to interpret. This is because any changes in disease epidemiology observed may be more an artefact of changes in the sensitivity of the system rather than a true change in disease.

Another limitation was the acceptability of the NNDSSVZV. The representativeness of the surveillance system could be improved if NSW began notifying disease; however, there was a low acceptance of the utility of the current system. A number of notifying jurisdictions also questioned the utility of the system and consequently suggested that the acceptability of the NNDSSVZV was not high. There were a number of stakeholders who mentioned that other data sources should be considered instead of using the NNDSSVZV. Moreover, some stakeholders were not aware of any reports using data from the NNDSSVZV. Without knowledge of public health action or the implementation of public health policy, acceptability is likely to be even poorer.

Measuring vaccine effectiveness was described as an objective of the NNDSSVZV. Due to the poor sensitivity of the surveillance system, vaccine effectiveness cannot be measured reliably. A previous publication discussed observational study methods used to calculate vaccine effectiveness and concluded that cohort studies during outbreak investigations are the simplest and most accurate of observational study designs in calculating vaccine effectiveness.⁶⁹ Cohort studies have previously been conducted in Australia to calculate varicella vaccine effectiveness.^{61, 70} Conducting retrospective cohort studies during outbreaks may be a better approach in achieving this objective compared to using notification data.⁶⁹

Other data sources to meet the system's objectives

From stakeholder responses, it was stated that other data sources are needed to compliment the NNDSSVZV and perhaps be better alternatives to the current system. However, the strengths and limitations of these data sources, in the context of the evaluation of the NNDSSVSV need to be considered.

PAEDS data

The PAEDS data provided an important data source to examine severe cases of VZV in infants and children using an active surveillance system and to compare with the NNDSSVZV. Comparisons made between NNDSSVZV data and PAEDS data

highlighted that even severe paediatric cases of varicella, specifically chickenpox cases were not notified to the NNDSS. Additionally, it identified that a positive test result was significantly associated with whether it was notified to health authorities. This is of concern, given that in a number of instances, specimens could not be taken to confirm a diagnosis. It has been emphasised in this evaluation that the purpose of the NNDSSVZV is not to capture every case of chickenpox or shingles, nationally, rather, the system should be sensitive in capturing severe varicella cases, which from our results the notification system is not achieving.

To interpret PAEDS data, it was important to consider the limitations of the PAEDS dataset. Firstly, data were from three separate paediatric hospitals, which may have affected the representativeness of severe varicella cases in children. The three hospitals were large paediatric tertiary hospitals and likely to be representative of their states, moreover, the objective of analysing PAEDS data was to calculate proportions of PAEDS cases that were notified to the NNDSSVZV, which could be calculated regardless of the representativeness.

Additionally, a number of changes to the case definition for VZV infection have occurred in the PAEDS data since 2007 (personal communication: Jocelynn McRae, PAEDS). Prior to November 2012, the age of cases collected was between >1 month and 14 years. In November 2012, the age of cases was lowered to include neonates (infants < 1month old). Also, cases could also include individuals without complications. For this evaluation, data were collected until December 2012 (one month of data where the case definition was different). There were only five PAEDS cases between in December 2012, and all were >1 month of age; of which four suffered complications. The change in case definition may have led to only one additional case during our study period so was thus unlikely to have affected our results.

A case definition to include herpes zoster infection was only officially applied in May 2013, and hence it is difficult to interpret shingles cases from the PAEDS dataset as it was likely to be underreported. Furthermore, shingles cases may have been reported as a 'complication' of varicella. The PAEDS network was not explicitly intended to capture herpes zoster cases and thus may not have reported consistently resulting in a possible underestimation of shingles cases. This change occurred after our study period; and whether the case was chickenpox or shingles should not impact on the main finding from the PAEDS data; that is, a positive test result was an important determinant to whether a PAEDS case was notified to health authorities.

Laboratory diagnoses were also limited by the inability to obtain vesicle fluid as the vesicles had healed by the time of hospitalisation. Although a clinical diagnosis of chickenpox or shingles may lead to false positives, this was unlikely given the characteristic illness of disease and also that cases were admitted to tertiary paediatric hospitals where paediatricians were highly experienced. Despite the limitations outlined above, PAEDS provided an important data source to assess the sensitivity of the NNDSSVZV, particularly in collecting information on severe cases of disease in children.

BEACH data

The analysis of BEACH data enabled the community burden of chickenpox and shingles to be examined. When comparing disease in a community setting to NNDSSVZV data, a number of conclusions were established. Firstly, requests for laboratory confirmation of chickenpox and shingles were poor, particularly in the ages <5 years and 60+ age groups. In contrast, test requests between 5–59 years were increasing over time and much higher than the other two age groups, which suggested that there was uncertainty in making a clinical diagnosis for this age group. Secondly, over the 13-year period from the BEACH data, only eight PCR test requests were made for shingles encounters. Given that PCR was the main laboratory test method for chickenpox and shingles in the NNDSSVZV, it indicated that the sensitivity of the NNDSSVZV was extremely low i.e. the cases collected in the BEACH dataset would not have been captured in the NNDSS dataset. Despite the poor sensitivity, the pattern of disease between the two data sources was similar, particularly in children 1–4 years and 5–9 years. Similarly, for shingles, the comparison between BEACH and NNDSS data suggested that the NNDSSVZV was sensitive in capturing community disease patterns in all age groups over 30 years.

BEACH data were found to be an important data source in examining varicella disease in the community, particular as data has been available since 1998 (pre-vaccine). BEACH data were obtained from 1000 randomly selected GPs that differ every year.⁷¹ Although the response rate was 30%, comparisons of the sampling frame using Medicare data occurred and led to adjustments to ensure the BEACH sample was representative of GP activity in Australia.⁷¹ Furthermore, although BEACH use a clustered sample study design (100 consecutive encounters per GP), rates were adjusted to account for the cluster design.⁷¹

A number of limitations of the data need to be considered in the context of comparison with NNDSS data. A limitation of the study was that NNDSSVZV data and BEACH data years were compared using different months (i.e. January to December versus April to March, respectively). The seasonality of disease patterns from the NNDSSVZV were examined and based on the peaks observed, would not have affected the analysis. From our results, the number of disease encounters stratified by age group was quite small which contributed to the considerable fluctuations in rates of disease in the BEACH data, making it difficult to monitor varicella in the community. Lastly, a patient may have been double counted if they returned to their GP within the 100 encounters captured by a GP, overestimating the encounters associated with chickenpox or shingles. New and total encounters were collected to overcome this possible overestimation and to determine if there was a difference in rates between the two.

NSW EDDC data

It was important to examine the burden of disease in NSW to provide an understanding of the patterns of chickenpox and shingles occurring in a significant proportion of the Australian population. By comparing NSW ED data and NNDSSVZV data, it was possible not only to consider the sensitivity of the NNDSSVZV in capturing the patterns of disease from a well-established data source that existed prior to the vaccine program implementation, but also to assess the representativeness of the NNDSSVZV. NSW not notifying VZV disease was considered to be a major impediment in interpreting NNDSSVZV as it would not be representative of the national picture of disease. From the comparisons in this study however, it suggested the opposite. That even without NSW notifying, the NNDSSVZV was capturing trends in disease that was similar to NSW and hence was representative in capturing disease trends at a national level.

An important limitation to consider in interpreting ED data was the participation of EDs in the NSW ED Data Collection (EDDC) database. Participation of EDs increased over time, from 46 EDs participating in 1996 to 97 EDs in 2013 (personal communication: Sophie Norton, NSW Ministry of Health). Data analysed in this report included only 46 EDs that consistently participated during 1998 to 2011. Data were only analysed from these hospitals to ensure increases in rates of disease was not associated with an increase in participation for a particular year. Approximately 150 public hospital EDs exist in NSW, and therefore it was possible that the reporting EDs used in this evaluation was not representative. Moreover, the EDDC database does not collect any data from private hospitals. Although this may mean that the rates of disease were an

underestimate, further exacerbated by the use of the total NSW population as the denominator in estimating rates, the consistency in the numerator (disease from the 46 EDs) and denominator (NSW population) would still have captured changes in disease patterns. Moreover, most of the larger EDs in the state are participants of EDDC resulting in a large proportion of the NSW population being covered by this system and hence likely to be a representative system. An important consideration of the NSW EDDC dataset is that variation on completeness of diagnosis reporting occurred over time in some hospitals of which the extent of this is unknown.

Recommendations

Following this evaluation, CDNA may want to consider the following recommendations to assist the NNDSSVZV in meeting its objectives and improving the system's attributes.

1. Consistent follow-up of chickenpox and shingles notifications. Currently, follow-up of cases varies substantially by jurisdiction. The inability to determine whether a notification was chickenpox or shingles hampers the ability to interpret NNDSS data.
2. Demographic information is not collected e.g. vaccination status in a number of jurisdictions to aid the system in meeting its objectives. To improve this, a number of options exist including:
 - Provide more resources for states and territories to conduct follow-up, however this needs to be considered in the context of other issues that may be of greater public health importance in each jurisdiction.
 - Update laboratory reporting forms to include a field indicating whether the test is for chickenpox or shingles and also what the patient's vaccination status is.
 - Develop an automated communication system for all VZV unspecified cases and cases missing vaccination status to automatically follow-up clinicians. A standardised varicella-specific follow-up form could be sent to clinicians through a fax or email system that does not require any extra time of surveillance staff.
3. Revise the national case definitions for chickenpox, shingles and unspecified disease to include VZV positive test results obtained in a CSF specimen as a case of disease.
4. Audit the data extraction process between jurisdictions and the Commonwealth in light of the poor completeness of vaccination status observed in one jurisdiction known to conduct comprehensive follow-up in children ≤ 7 years.
5. Consistent application of the case definitions so that a clinically diagnosed case of chickenpox and shingles without laboratory evidence and without an epidemiological link are considered probable cases.
6. Recommend NSW make VZV notifiable to improve the representativeness of the NNDSSVZV which will allow for a better understanding of the burden of chickenpox and shingles. This is of particular importance in light of the increased availability of zoster vaccine.

7. Development of a national guideline to guide jurisdictions in follow-up including implementing control and preventative measures, particularly in response to the anticipated decline in incidence of chickenpox following the vaccine program implementation.
8. For future vaccine preventable diseases, a strategy should be in place to establish surveillance to assess the impact of universal vaccine, prior to the implementation of the vaccine program.

Conclusions

The surveillance system for chickenpox and shingles in Australia does not appear to meet its main objective of measuring the impact of universal varicella vaccine. Although notification rates on chickenpox and shingles are being captured by the current NNDSSVZV, the poor sensitivity and the non-existence of notification rates pre-vaccine limits the utility of the system. Resources among jurisdictions are a major barrier to improving the NNDSSVZV, due to limited capacity to conduct follow-up which has compromised the sensitivity and quality of the data. A review of the case definition and standardised reporting is recommended to ensure that consistency among jurisdictions will allow for the accurate interpretation of data.

References

1. Gershon A, Takahashi M, Seward J. Varicella vaccine. In: Plotkin SA, Orenstein WA, Offit PA, editors. *Vaccines*. 6th ed. Philadelphia: Saunders Elsevier; 2013.
2. Centers for Disease Control and Prevention (CDC). Varicella. In: Atkinson W, Wolfe C, Hamborsky J, editors. *Epidemiology and prevention of vaccine-preventable diseases*. 12th edition, second printing ed. Washington, D.C.: Public Health Foundation; 2012.
3. Heininger U, Seward JF. Varicella. *Lancet*. 368(9544):1365-76.
4. Guess H, Broughton D, Melton Lr, Kurland L. Population-based studies of varicella complications. *Pediatrics*. 1986;78(4):723-7.
5. Choo PW, Donahue JG, Manson JE, Platt R. The epidemiology of varicella and its complications. *Journal of infectious diseases*. 1995;172(3):706-12.
6. Centers for Disease Control and Prevention (CDC). Prevention of Varicella. *MMWR*. 2007;56:1-38.
7. Kimberlin DW, Whitley RJ. Varicella-zoster vaccine for the prevention of herpes zoster. *New England Journal of Medicine*. 2007;356(13):1338-43.
8. Heymann DL. *Control of communicable diseases manual*. 19th ed: American Public Health Association; 2008.
9. Stein AN, Britt H, Harrison C, Conway EL, Cunningham A, MacIntyre CR. Herpes zoster burden of illness and health care resource utilisation in the Australian population aged 50 years and older. *Vaccine*. 2009;27(4):520-9.
10. National Health and Medical Research Council. *The Australian immunisation handbook*. 10th edition. Canberra 2013.
11. Gershon AA. Varicella-zoster virus infections. *Pediatrics in Review*. 2008;29(1):5-11.
12. Leung J, Harpaz R, Baughman AL, Heath K, Loparev V, Vazquez M, et al. Evaluation of Laboratory Methods for Diagnosis of Varicella. *Clinical Infectious Diseases*. 2010;51(1):23-32.
13. Antibiotic Expert Group. *Therapeutic guidelines: antibiotic*. Melbourne: Therapeutic Guidelines Limited; 2010.
14. Government of Western Australia Department of Health. *Virus Watch*. 2013 [updated 24 March 2013; cited 2013 3 April]; Available from: http://www.public.health.wa.gov.au/3/487/3/virus_watch.pm.
15. Takahashi M, Otsuka T, Okuno Y, Asano Y, Yazaki T, Isomura S. Live vaccine used to prevent spread of varicella in children in hospital. *Lancet*. 1974;2(7892):1288-90.
16. Dworkin MS, Jennings CE, Roth-Thomas J, Lang JE, Stukenberg C, Lumpkin JR. An outbreak of varicella among children attending preschool and elementary school in Illinois. *Clinical infectious diseases*. 2002;35(1):102-4.
17. Galil K, Lee B, Strine T, Carraher C, Baughman AL, Eaton M, et al. Outbreak of varicella at a day-care center despite vaccination. *New England Journal of Medicine*. 2002;347(24):1909-15.
18. Tugwell BD, Lee LE, Gillette H, Lorber EM, Hedberg K, Cieslak PR. Chickenpox outbreak in a highly vaccinated school population. *Pediatrics*. 2004;113(3):455-9.
19. Lopez AS, Guris D, Zimmerman L, Gladden L, Moore T, Haselow DT, et al. One dose of varicella vaccine does not prevent school outbreaks: is it time for a second dose? *Pediatrics*. 2006;117(6):e1070-e7.
20. Centers for Disease Control and Prevention (CDC). Prevention of varicella: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2007;56(RR-04):1-40.
21. Kuter B, Matthews H, Shinefield H, Black S, Dennehy P, Watson B, et al. Ten year follow-up of healthy children who received one or two injections of varicella vaccine. *Pediatric Infectious Disease Journal*. 2004;23(2):132-7.

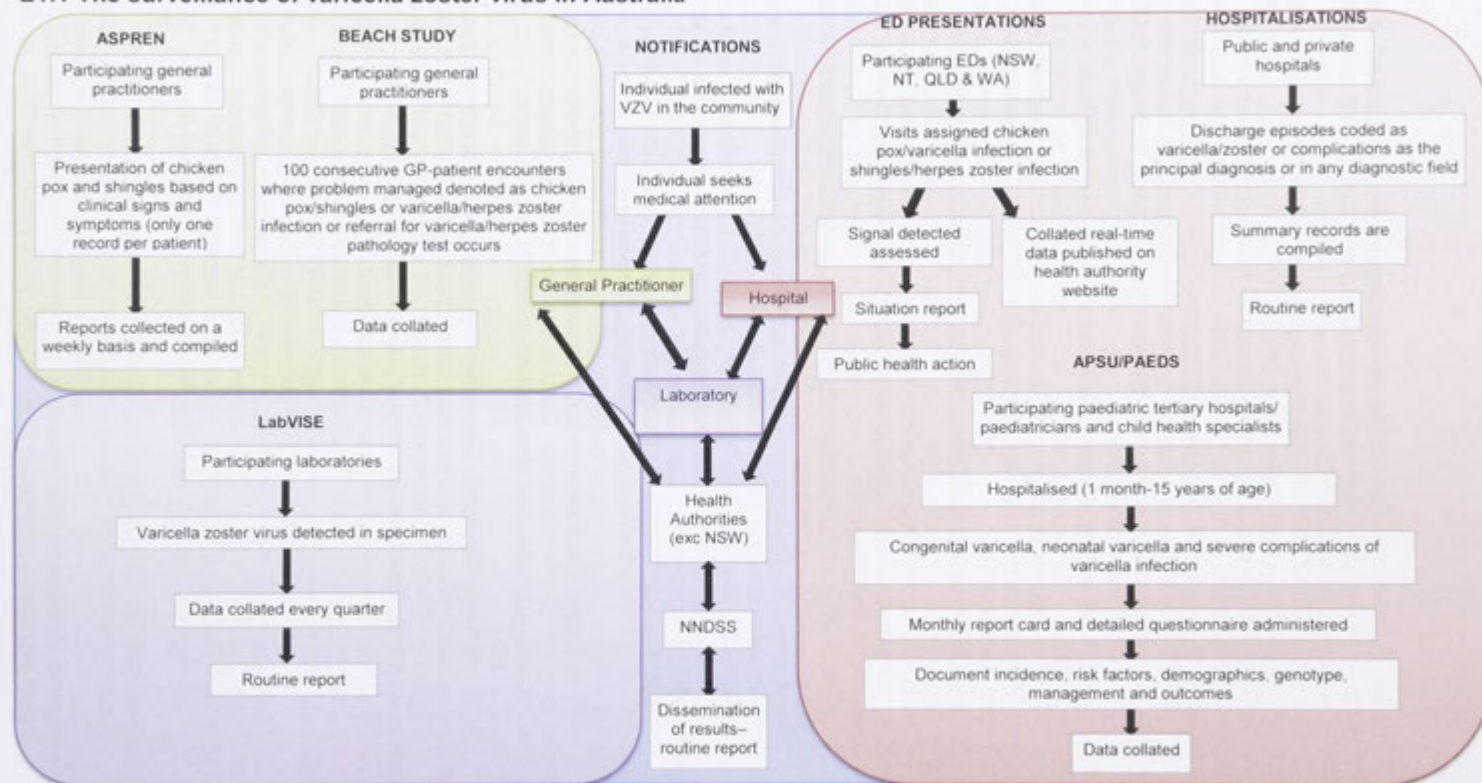
22. National Centre for Immunisation Research and Surveillance of Vaccine Preventable Diseases. Significant events in varicella vaccination practice in Australia. 2012 [updated June 2012; cited 2013 28 January]; Available from: <http://www.ncirs.edu.au/immunisation/history/Varicella-history-June-2012.pdf>.
23. Ward K, Quinn HE, Bachelor M, Bryant V, Campbell-Lloyd S, Newbound A, et al. Adolescent school-based vaccination in Australia. *Commun Dis Intell*. 2013;37(2):E156-E67.
24. Department of Health and Ageing. National Immunisation Program Schedule. 2011 [updated 15 June, 2012 cited 2012 20 July]; Available from: <http://immunise.health.gov.au/internet/immunise/publishing.nsf/Content/nips2>.
25. Department of Health and Ageing. Strengthening Immunisation for Children. [updated 25 Nov 2011; cited 2013 13 Feb]; Available from: <http://immunise.health.gov.au/internet/immunise/publishing.nsf/Content/factsheet-strengthening-immunisation>.
26. National Centre for Immunisation Research and Surveillance of Vaccine Preventable Diseases. Zoster Vaccine for Australian Adults: Information for Immunisation Providers. 2009 [cited 2013 15 January]; Available from: <http://www.ncirs.edu.au/immunisation/fact-sheets/herpes-zoster-vaccine-fact-sheet.pdf>.
27. Roche P, Blumer C, Spencer J. Surveillance of viral pathogens in Australia: Varicella-zoster virus. *Communicable Diseases Intelligence Quarterly Report*. 2002;26(4):576.
28. Givney R. Varicella surveillance: simpler than you think? *Commun Dis Intell*. 2003;27:100-1.
29. NNDSS Annual Report Writing Group. Australia's Notifiable Disease Status, 2009: Annual Report of the National Notifiable Diseases Surveillance System. *Communicable Diseases Intelligence*. 2011;35(2):61-131.
30. Liu C, Stirzaker S, Knuckey D, Robinson K, Knope K, Fitzsimmons G, et al. Australia's notifiable disease status, 2007: annual report of the National Notifiable Diseases Surveillance System. *Commun Dis Intell*. 2009;33(2):89-154.
31. NSW Ministry of Health. Emergency department visits assigned a diagnosis of chickenpox or varicella infection in NSW residents. 2013 [updated 24 March 2013; cited 2013 25 March]; Available from: <http://www0.health.nsw.gov.au/data/diseases/chickenpox.asp>.
32. NSW Ministry of Health. Emergency department visits assigned a diagnosis of shingles or herpes zoster disease in NSW residents. 2013 [updated 24 March 2013; cited 2013 25 March]; Available from: <http://www0.health.nsw.gov.au/data/diseases/shingles.asp>.
33. Macintyre CR, Chu CP, Burgess MA. Use of hospitalization and pharmaceutical prescribing data to compare the prevaccination burden of varicella and herpes zoster in Australia. *Epidemiology and Infection*. 2003;131(1):675-82.
34. Department of Health and Ageing. Vaccine Preventable Diseases in Australia, 2005-2007. *Communicable Diseases Intelligence*. 2010;34 (Supplement).
35. Roche P, Halliday L, O'Brien E, Spencer J. The laboratory virology and serology reporting scheme, 1991 to 2000. *Communicable diseases intelligence*. 2002;26(3):323-73.
36. Surveillance systems reported in CDI, 2012. *Commun Dis Intell*. 2012;36(1):122.
37. Fielding J. Evaluation of varicella-zoster surveillance in South Australia [MAE]. Canberra: Australian National University; 2005.
38. Chant KG, Sullivan EA, Burgess MA, Ferson MJ, Forrest JM, Baird LM, et al. Varicella-zoster virus infection in Australia. *Australian and New Zealand Journal of Public Health*. 1998;22(4):413-8.
39. Peadon E, Burgner D, Nissen M, Buttery J, Zurynski Y, Elliott E, et al. Case for varicella surveillance in Australia. *Journal of Paediatrics & Child Health*. 2006;42(11):663-4.

40. Forrest JM, Mego S, Burgess MA. Congenital and neonatal varicella in Australia. *Journal of Paediatrics & Child Health*. 2000;36(2):108-13.
41. Paediatric Active Enhanced Disease Surveillance (PAEDS) :Study Protocol – Varicella. 2013 [cited 2013 8 February]; Available from: <http://www.apsu.org.au/assets/PAEDS/PAEDS-Severe-varicella-protocol-v4.21.pdf>.
42. Gidding HF, Brisson M, MacIntyre CR, Burgess MA. Modelling the impact of vaccination on the epidemiology of varicella zoster virus in Australia. *Australian & New Zealand Journal of Public Health*. 2005;29(6):544-51.
43. Boughton C. Varicella-zoster vaccine [editorial]. *Med J Aust*. 1993;159:439-40.
44. McIntyre P, Amin J, Gidding H, Hull B, Torvaldsen S, Tucker A, et al. Vaccine preventable diseases and vaccination coverage in Australia, 1993-1998. *Communicable Diseases Intelligence*. June 2000((Supplement)).
45. Carapetis JR, Russell DM, Curtis N. The burden and cost of hospitalised varicella and zoster in Australian children. *Vaccine*. 2004;23(6):755-61.
46. Scuffham PA, Lowin A, Burgess M. The cost-effectiveness of varicella vaccine programs for Australia. *Vaccine*. 1999;18(5):407-15.
47. Seward JF, Zhang JX, Maupin TJ, Mascola L, Jumaan AO. Contagiousness of varicella in vaccinated cases. *JAMA: the journal of the American Medical Association*. 2004;292(6):704-8.
48. Gao Z, Gidding H, Wood J, Macintyre C. Modelling the impact of one-dose vs. two-dose vaccination regimens on the epidemiology of varicella zoster virus in Australia. *Epidemiology and Infection*. 2010;138(4):457.
49. Cunningham AL, Breuer J, Dwyer DE, Gronow DW, Helme RD, Litt JC, et al. The prevention and management of herpes zoster. *Medical Journal of Australia*. 2008;188(3):171-6.
50. Hope-Simpson RE. The nature of herpes zoster: a long-term study and a new hypothesis. *Proceedings of the Royal Society of Medicine*. 1965;58(1):9.
51. Nelson MR, Britt HC, Harrison CM. Evidence of increasing frequency of herpes zoster management in Australian general practice since the introduction of a varicella vaccine. *Medical Journal of Australia*. 2010;193(2):110-3.
52. Carville KS, Riddell MA, Kelly HA. A decline in varicella but an uncertain impact on zoster following varicella vaccination in Victoria, Australia. *Vaccine*. 2010;28(13):2532-8.
53. Swan W. Australia to 2050: future challenges In: Department A-Gs, editor. Barton, ACT2010.
54. Centers for Disease Control and Prevention (CDC). Evaluation of varicella reporting to the National Notifiable Disease Surveillance System- United States, 1972-1997. *MMWR*. 1999;48(3):55-8.
55. German RR, Lee L, Horan J, Milstein R, Pertowski C, Waller M. Updated guidelines for evaluating public health surveillance systems. *MMWR*. 2001;50:1-35.
56. Health Surveillance Coordinating Committee. Framework and tools for evaluating health surveillance systems. Vancouver: Health Canada; 2004; Available from: publications.gc.ca/collections/Collection/H39-4-46-2004E.pdf
57. Heywood AE, Macartney KK, Wang H, McIntyre P. Impact of varicella vaccination on hospitalisations: is high coverage with one dose enough? 2013.
58. Miller M, Roche P, Spencer J, Deebie M. Evaluation of Australia's national notifiable disease surveillance system. *Communicable diseases intelligence*. 2004;28:311-23.
59. NNDSS Annual Report Writing Group -. Australia's Notifiable Disease Status, 2010: Annual Report of the National Notifiable Diseases Surveillance System. *Communicable Diseases Intelligence*. 2012;36(1).
60. Department of Health and Ageing. Australian national notifiable diseases case definitions. [updated 15 July 2013; cited 2013 17 September]; Available from: <http://www.health.gov.au/casedefinitions>.

61. Reddel S. Assessment and cohort investigation of a varicella outbreak at a boarding school for year nine students in rural alpine Victoria, June 2011. Canberra Australian National University; 2011.
62. Dwyer DE, Cunningham AL. 10: Herpes simplex and varicella-zoster virus infections. *The Medical journal of Australia*. 2002;177(5):267.
63. Department of Health and Ageing. Varicella Zoster Virus Laboratory Case Definition 2009 [updated 12 April 2010; cited 2013 10 September]; Available from: <http://www.health.gov.au/internet/main/publishing.nsf/content/cda-phlncd-varicella>.
64. Department of Health and Ageing. Australian national notifiable diseases case definitions: Varicella-zoster infection (chickenpox). 2008 [updated 14 August 2008; cited 2013 7 March]; Available from: <http://www.health.gov.au/internet/main/publishing.nsf/Content/cdna-casedef-chickenpox.htm>.
65. Department of Health and Ageing. Australian national notifiable diseases case definitions: Varicella-zoster infection (shingles). 2008 [updated 7 November 2008; cited 2013 2 April]; Available from: <http://www.health.gov.au/internet/main/publishing.nsf/Content/cdna-casedef-shingles.htm>.
66. Department of Health and Ageing. Australian national notifiable diseases case definitions: Varicella-zoster infection (unspecified). 2008 [updated 7 November 2008; cited 2013 3 April]; Available from: <http://www.health.gov.au/internet/main/publishing.nsf/Content/cdna-casedef-varicella-unspec.htm>.
67. Wehrhahn M, Dwyer D. Herpes zoster: epidemiology, clinical features, treatment and prevention. *Australian Prescriber*. 2012;35(5):143-7.
68. Opstelten W, van Loon AM, Schuller M, van Wijck AJ, van Essen GA, Moons KG, et al. Clinical diagnosis of herpes zoster in family practice. *The Annals of Family Medicine*. 2007;5(4):305-9.
69. Torvaldsen S, McIntyre PB. Observational methods in epidemiologic assessment of vaccine effectiveness. *Communicable diseases intelligence*. 2002;26(3):451-7.
70. Vally H, Dowse GK, Eastwood K, Cameron S. An outbreak of chickenpox at a child care centre in Western Australia. Costs to the community and implications for vaccination policy. *Australian and New Zealand Journal of Public Health*. 2007;31(2):113-9.
71. Britt H, Miller G, Bayram C. The quality of data on general practice-a discussion of BEACH reliability and validity. *Australian family physician*. 2007;36(1-2):36.
72. Zurynski Y, Elliott E, Groenendyk T, Ridley G (Eds). *Australian Paediatric Surveillance Unit Biennial Research Report 2009 and 2010*. Sydney: 2012.

Appendix E

E1.1 The surveillance of varicella zoster virus in Australia



E1.2. Australian national notifiable disease case definitions

| | |
|--------------------------------------|--|
| Varicella zoster (chickenpox) | <p><u>Confirmed case</u></p> <p>Laboratory definitive AND clinical evidence OR Clinical AND epidemiological evidence</p> <p><u>Probable case</u></p> <p>Clinical evidence only</p> <hr/> <p><u>Laboratory definitive evidence</u> Isolation of varicella-zoster virus from a skin or lesion swab OR detection of varicella-zoster virus by nucleic acid testing from a skin or lesion swab OR detection of varicella-zoster virus antigen by direct fluorescent antibody from a skin or lesion swab OR detection of varicella-zoster virus-specific IgM in an unvaccinated person. If the case received varicella vaccine between 5 and 42 days prior to the onset of rash the virus must be confirmed to be a wild type strain.</p> <p><u>Clinical evidence</u> Acute onset of a diffuse maculopapular rash developing into vesicles within 24–48 hours and forming crusts (or crusting over) within five days</p> <p><u>Epidemiological evidence</u> Contact between two people involving a plausible mode of transmission at a time when one of them is likely to be infectious AND the other has illness ten to 21 days after contact AND at least one case in the chain of epidemiologically-linked cases is laboratory confirmed.</p> |
| Varicella zoster (shingles) | <p><u>Confirmed case</u></p> <p>Laboratory definitive AND clinical evidence</p> <p><u>Probable case</u></p> <p>Clinical evidence only</p> <hr/> <p><u>Laboratory definitive evidence</u> Isolation of varicella-zoster virus from a skin or lesion swab OR detection of varicella-zoster virus from a skin or lesion swab by nucleic acid testing from a skin or lesion swab OR detection of varicella-zoster virus antigen from a skin or lesion swab by direct fluorescent antibody from a skin or lesion swab.</p> <p><u>Clinical evidence</u> A vesicular skin rash with a dermatomal distribution that may be associated with pain in skin areas supplied by sensory nerves of the dorsal root ganglia.</p> |

| | |
|---|--|
| Varicella zoster (unspecified) | <u>Confirmed case</u> Laboratory definitive in the absence of clinical evidence |
| | <u>Laboratory definitive evidence</u> Isolation of varicella-zoster virus from a skin or lesion swab OR detection of varicella-zoster virus from a skin or lesion swab by nucleic acid testing from a skin or lesion swab OR detection of varicella-zoster virus antigen from a skin or lesion swab by direct fluorescent antibody from a skin or lesion swab OR detection of varicella-zoster virus-specific IgM in an unvaccinated person. |

E2.1 Notifying Jurisdictional Stakeholder Questionnaire

Instructions on answering

- The National Centre for Immunisation Research and Surveillance (NCIRS) is currently undertaking an evaluation of the national varicella notification.
- The aim of the evaluation is to assess the current notification surveillance system for varicella zoster in Australia.
- All questions refer to varicella (chickenpox) and varicella (shingle) unless otherwise stated.
- All information you provide will be confidential and de-identified.
- The questionnaire should take approximately 15 minutes to complete.

Question 1. What jurisdiction are you from?

- ☐ Victoria
- ☐ Queensland
- ☐ South Australia
- ☐ Western Australia
- ☐ Tasmania
- ☐ Northern Territory
- ☐ Australian Capital Territory

Question 2. What is your role in varicella notifications in your jurisdiction?

Question 3. Within your jurisdiction, how is a confirmed varicella zoster (chickenpox) case defined?

This section aims to measure how well the objectives of the varicella notification system are being met.

Question 4. Please rate you \geq on the following objectives of the national notification of varicella:

| | Strongly agree | Agree | Neutral | Disagree | Strongly disagree |
|---|----------------|-------|---------|----------|-------------------|
| The incidence of varicella infection in the Australian is being measured. | | | | | |
| -specifically in unimmunised children | | | | | |
| -in unimmunised adults | | | | | |
| -in Indigenous children. | | | | | |
| -in Indigenous adults | | | | | |
| Vaccine effectiveness over time can be measure by age group. | | | | | |
| Vaccine effectiveness over time can be measured by vaccine schedule. | | | | | |
| The changes in the epidemiology of zoster in Australia are being monitored. | | | | | |

Further comments

Question 5. Apart from the objectives listed above, are there any other objectives of the varicella notification system that you can think of?

☐ Yes

☐ No

☐ Unsure

Question 6. Please list these objectives.

Question 7.

Are these objectives being met by the current varicella notification system?

- ☐ Yes
☐ No
☐ Unsure

USEFULNESS

This section aims to determine how helpful the notification system is to public health staff.

Question 8. Who are the main users of varicella notification data?

- ☐ Jurisdictional Surveillance Officers
☐ Jurisdictional Immunisation Coordinators
☐ Commonwealth Surveillance staff
☐ Commonwealth Immunisation staff
☐ Researchers
☐ Other

If other (please specify)

Question 9. What are the uses of notification data in your jurisdiction?

Question 10. Has national notification system for varicella led to public health action in the following?

| | Yes | No | Unsure |
|-------------------|-----|----|--------|
| Your jurisdiction | | | |
| National | | | |

Question 11. Please provide details (if relevant).

Question 12. Has the national notification system for varicella led to changes in public health policy in the following?

| | Yes | No | Unsure |
|-------------------|-----|----|--------|
| Your jurisdiction | | | |
| National | | | |

Question 13. Please provide details (if relevant).

Question 14. To your knowledge, has varicella notifications led to the generation of national reports?

- ☐ Yes
- ☐ No
- ☐ Unsure

Question 15. Please provide details.

Question 16. Does follow-up occur if the following individuals are notified varicella (chickenpox) cases?

| | Yes | No | Unsure |
|-------------------------|-----|----|--------|
| Neonates | | | |
| Infants | | | |
| Children aged 1—5 years | | | |
| School children | | | |
| Pregnant women | | | |
| Indigenous individuals | | | |
| Other | | | |

If other (please specify)

Question 17. If yes, please select what follow-up is conducted.

| | Yes | No | Unsure |
|------------------------------------|-----|----|--------|
| Case interview | | | |
| Clinician interview | | | |
| Verification of vaccination status | | | |

Other (please specify)

Question 18. If follow-up differs depending on groups specified in Question 17, please describe what differences exist.

Question 19. Are varicella (chickenpox) outbreaks that occur recorded by your jurisdiction.

- ☐ Yes
☐ No
☐ Unsure

Question 20. Please provide examples what information is collected.

Question 21. Do you collect any extra information from varicella cases that are not sent to the NNDSS?

- ☐ Yes
- ☐ No
- ☐ Unsure

Question 22. Please provide details.

ACCEPTABILITY

The aim of this section is to measure how willing you are to participate in the current notification system.

Question 23. In your view, please rate the public health importance of varicella

- ☐ Extremely important
- ☐ Important
- ☐ Neutral
- ☐ Unimportant
- ☐ Extremely unimportant

Question 24. Do you think notifying varicella is a good use of you time?

- ☐ Yes
- ☐ No
- ☐ Unsure

Question 25. Please provide details (if any).

Question 26. Do you think the current requirements for varicella (chickenpox) case reporting in States and Territories is adequate?

- ☐ Yes
- ☐ No
- ☐ Unsure

Question 27. Please provide details.

Question 28. What do you think could be done to improve the acceptability of the national varicella notification system?

SIMPLICITY

This section aims to ascertain the structure of the system and its ease of operation.

Question 29. Please describe how varicella notification data gets from your jurisdiction to the national system.

Question 30. Compared to other notifiable disease, is it easy to report varicella to the NDDSS?

- ☐ Yes
☐ No
☐ Unsure

Question 31. Please give your reasons.

Question 32. Do you think that the flow of information on varicella notifications to and from the NNDSS is adequate?

- ☐ Yes
☐ No
☐ Unsure

Question 33. Please provide details.

Question 34. What are the reasons for not making varicella notifiable in your jurisdiction?

This section seeks information on your views on the national notification system for varicella.

Question 35. In your opinion, what are the strengths of the national system for varicella, for Australia overall?

Question 36. In your opinion, what are the limitations of the national notifications system for varicella, for Australia overall?

Question 37. In your opinion, how could the national varicella notification system be improved, for Australia overall?

Question 38. Do you think that varicella should be notifiable in your jurisdiction?

☐ Yes

☐ No

☐ Unsure

Question 39. Please give your reasons.

Question 40. Further comments.

Thank you for completing the questionnaire

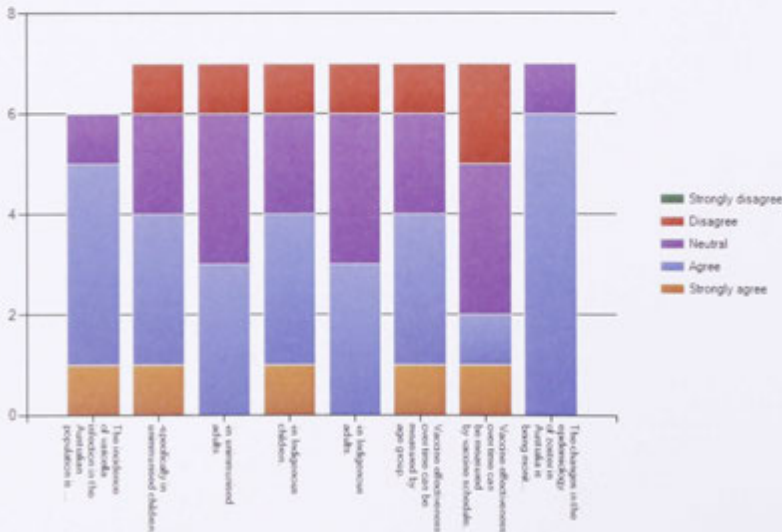
E2.2 Notifying jurisdictions quantitative responses from questionnaire

1. What jurisdiction are you from?

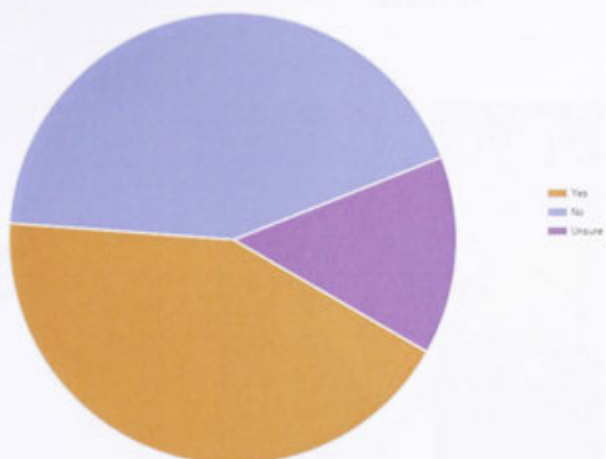
| | | |
|------------------------------|-------|---|
| Victoria | 14.3% | 1 |
| New South Wales | 0.0% | 0 |
| Queensland | 14.3% | 1 |
| South Australia | 14.3% | 1 |
| Western Australia | 14.3% | 1 |
| Tasmania | 14.3% | 1 |
| Northern Territory | 14.3% | 1 |
| Australian Capital Territory | 14.3% | 1 |

1. USEFULNESS

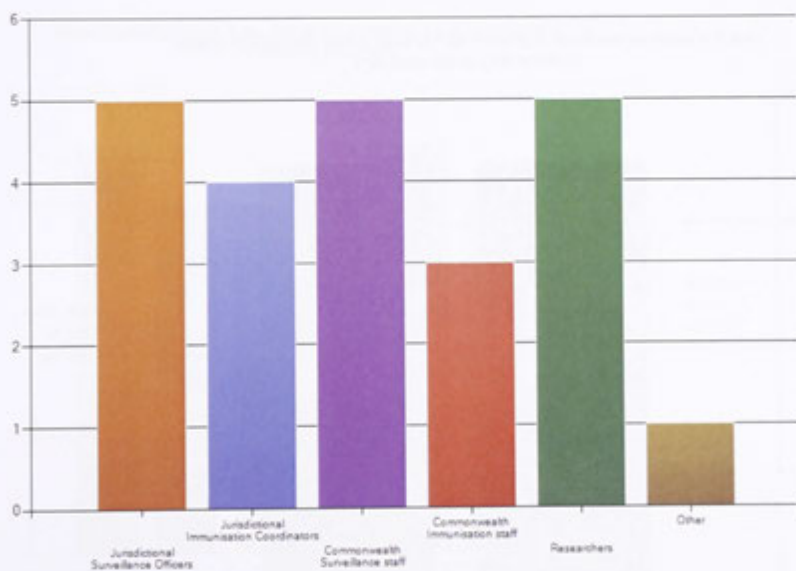
Please rate your agreement on the following objectives of the national notification of varicella:



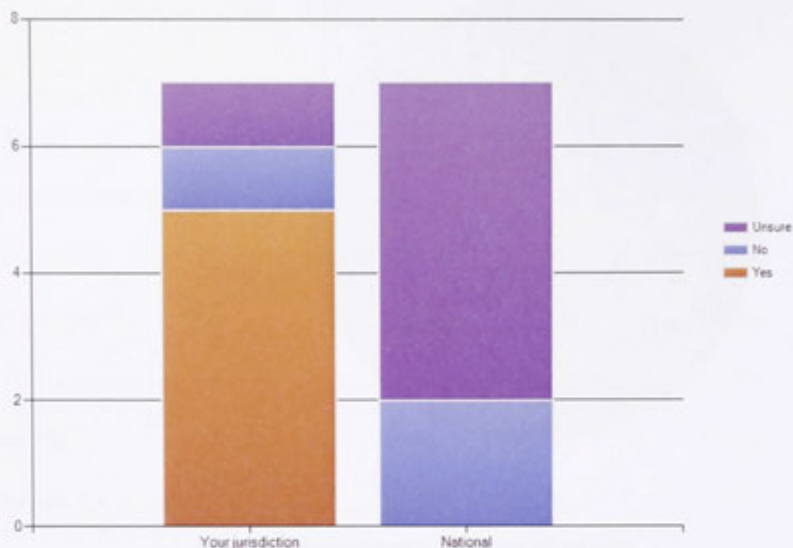
Apart from the objectives listed above, are there any other objectives of the varicella notification system that you can think of?



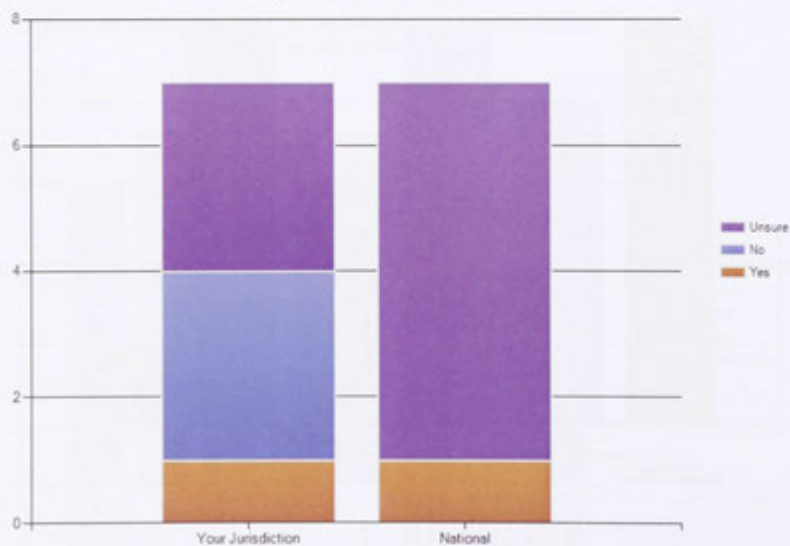
Who are the main users of varicella notification data?



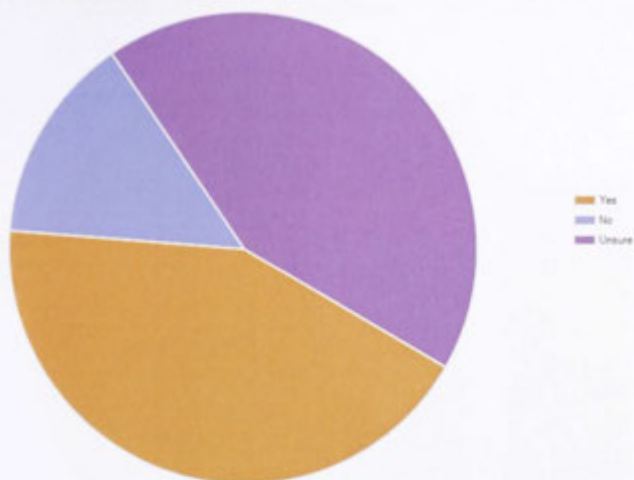
Has national notification system for varicella led to public health action in the following:



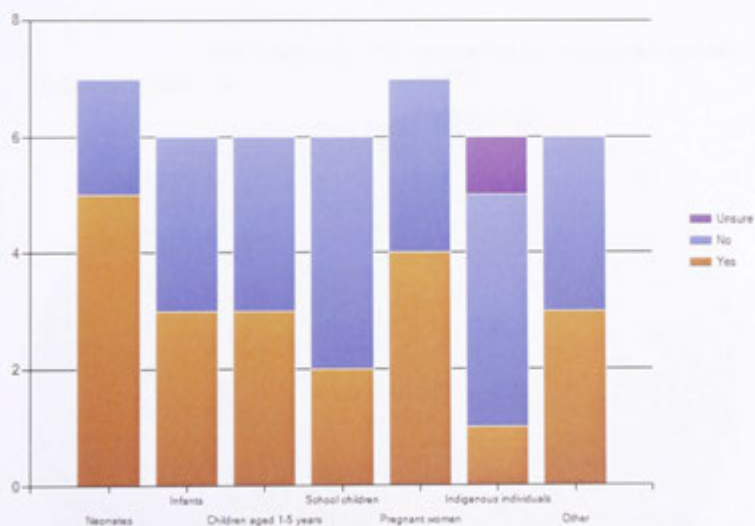
Has the national notification system for varicella led to changes in public health policy in the following



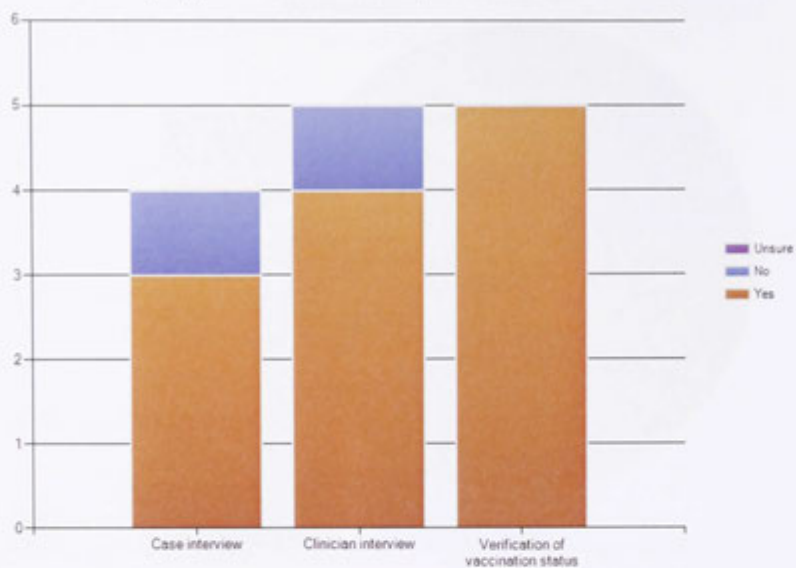
To your knowledge, has varicella notifications led to the generation of national reports?



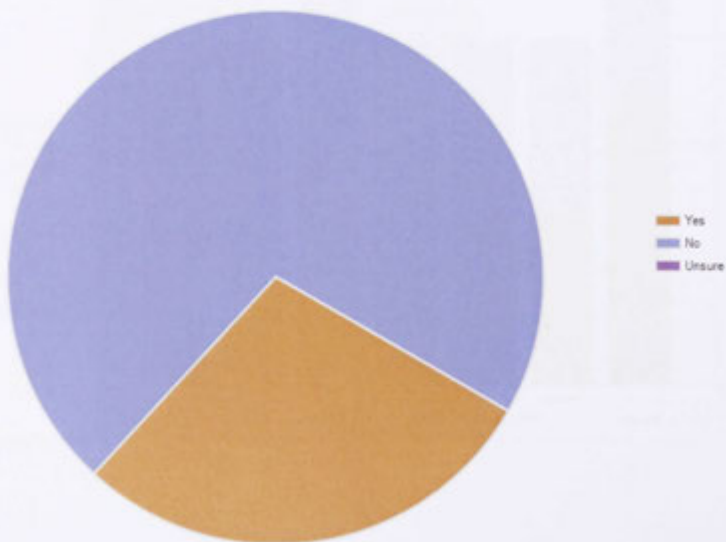
Does follow-up occur if the following individuals are notified varicella (chickenpox) cases?



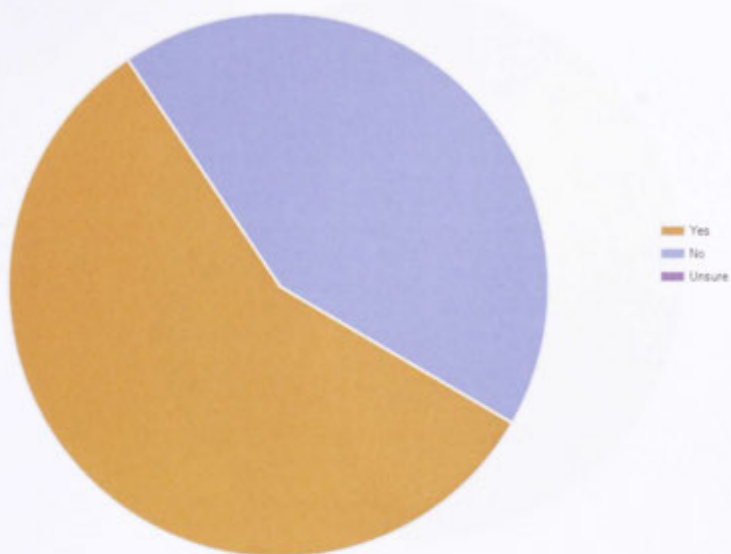
If yes, please select what follow-up is conducted.



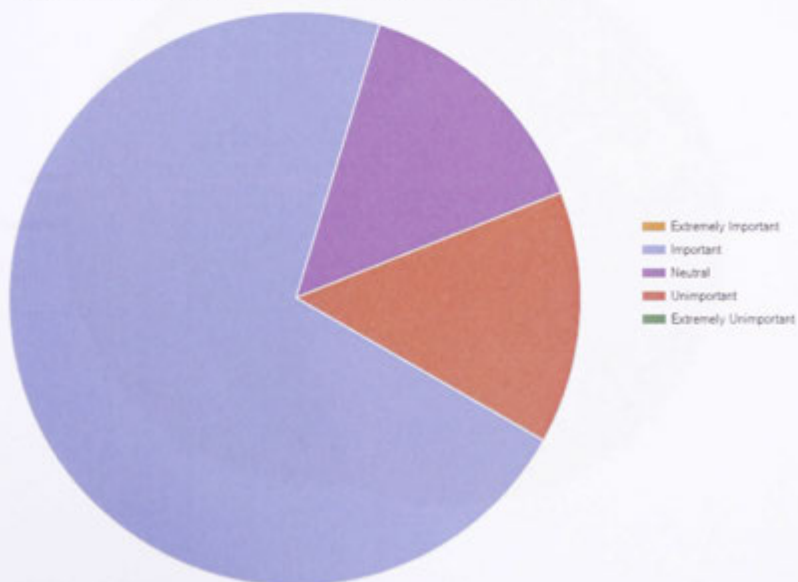
Are varicella (chickenpox) outbreaks that occur recorded by your jurisdiction?



Do you collect any extra information from varicella cases that is not sent to the NNDSS?

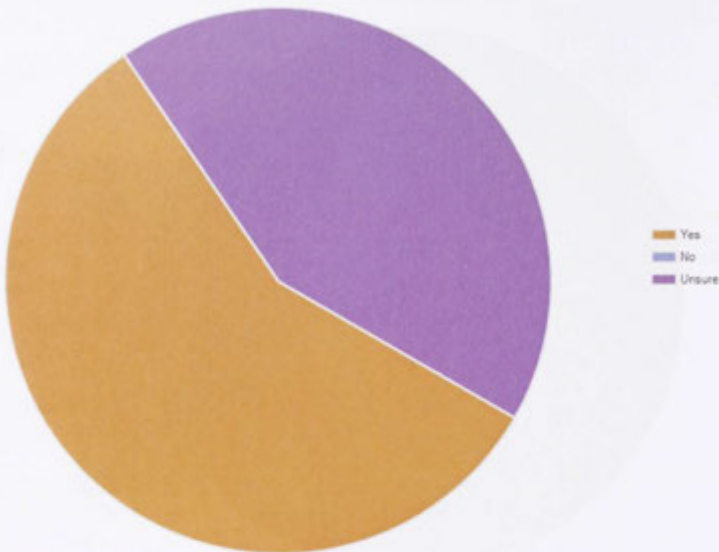


In your view, please rate the public health importance of varicella.

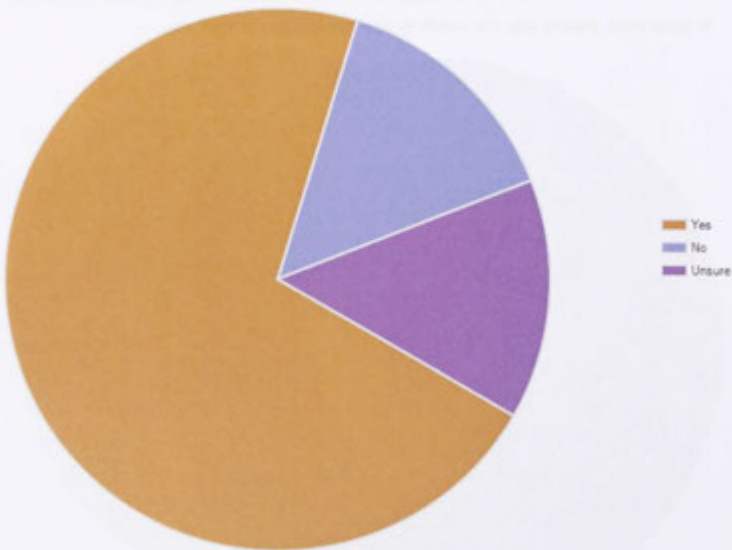


ACCEPTABILITY

Do you think notifying varicella is a good use of your time?

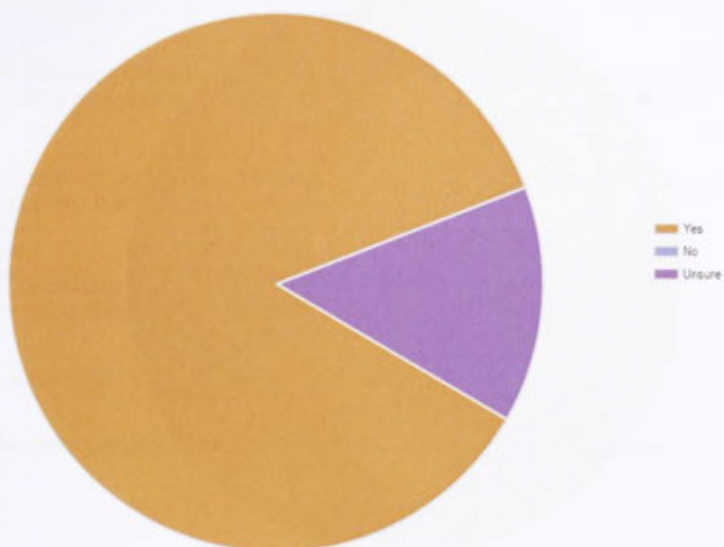


Do you think that the current requirements for varicella (chickenpox) case reporting in States and Territories is adequate?

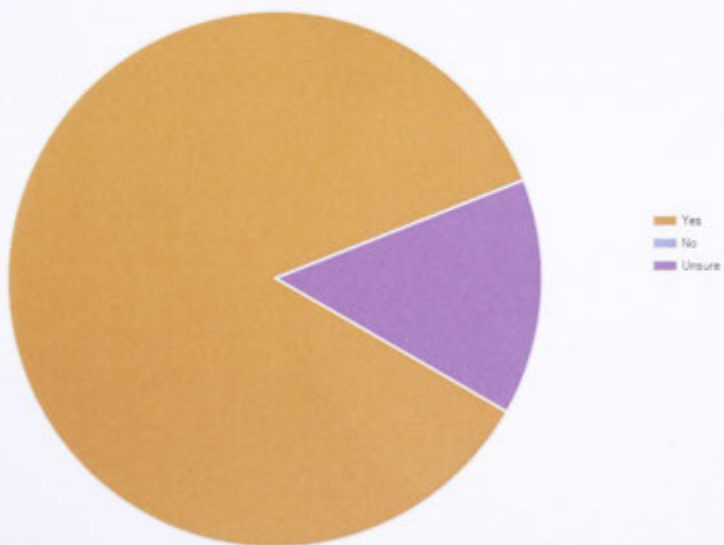


SIMPLICITY

Compared to other notifiable disease, is it easy to report varicella to the NNDSS?

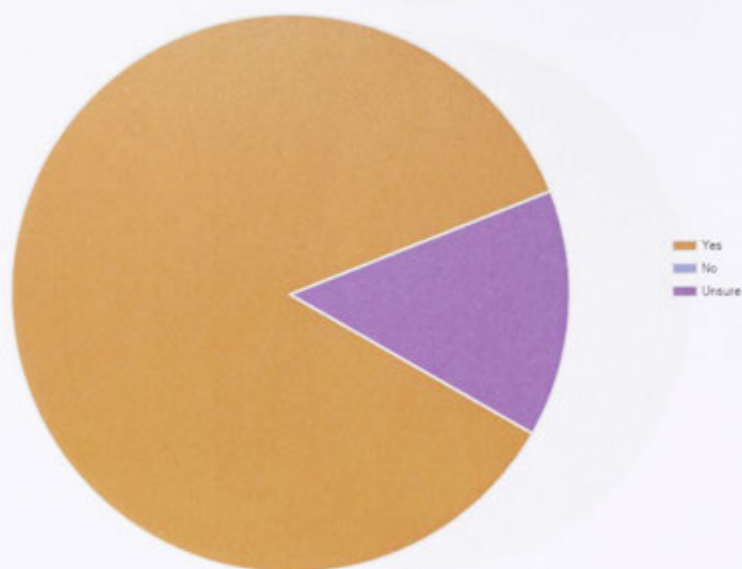


Do you think that the flow of information on varicella notifications to and from the NNDSS is adequate?



OTHER

Do you think that varicella should be notifiable in your jurisdiction?



E3.1 Non- Notifying Jurisdictional Stakeholder Questionnaire

Instructions on answering

- The National Centre for Immunisation Research and Surveillance (NCIRS) is currently undertaking an evaluation of the national varicella notification.
- The aim of the evaluation is to assess the current notification surveillance system for varicella zoster in Australia.
- All questions refer to varicella (chickenpox) and varicella (shingle) unless otherwise stated.
- All information you provide will be confidential and de-identified.
- The questionnaire should take approximately 5 minutes to complete.

Question 1. What are the reasons for not making varicella notifiable in your jurisdiction?

Question 2. In your opinion, what are the strengths of the national system for varicella, for Australia overall?

Question 3. In your opinion, what are the limitations of the national notification system for varicella, for Australia overall?

Question 4. In your opinion, how could the national varicella notification system be improved, for Australia overall?

Question 5. Do you think that varicella should be notifiable in your jurisdiction?

Question 6. Please give your reasons.

Question 7. Further comments.

Thank you for completing the questionnaire

E4.1 Commonwealth Stakeholder Questionnaire

Instructions on answering

- The National Centre for Immunisation Research and Surveillance (NCIRS) is currently undertaking an evaluation of the national varicella notification.
- The aim of the evaluation is to assess the current notification surveillance system for varicella zoster in Australia.
- All questions refer to varicella (chickenpox) and varicella (shingle) unless otherwise stated.
- All information you provide will be confidential and de-identified.
- The questionnaire should take approximately 15 minutes to complete.

Question 1. What is your role in varicella notifications in your jurisdiction?

Question 2. Please rate you agreement on the following objectives of the national notification of varicella:

| | Strongly agree | Agree | Neutral | Disagree | Strongly disagree |
|---|----------------|-------|---------|----------|-------------------|
| The incidence of varicella infection in the Australian is being measured. | | | | | |
| -specifically in unimmunised children | | | | | |
| -in unimmunised adults | | | | | |
| -in Indigenous children. | | | | | |
| -in Indigenous adults | | | | | |
| Vaccine effectiveness over time can be measure by age group. | | | | | |
| Vaccine effectiveness over time can be measured by vaccine schedule. | | | | | |
| The changes in the epidemiology of zoster in Australia are being monitored. | | | | | |

Further comments

Question 3. Apart from the objectives listed above, are there any other objectives of the varicella notification system that you can think of?

- ☐ Yes
- ☐ No
- ☐ Unsure

Question 4. If yes, please list these objectives.

Question 5. Are these objectives being met by the current varicella notification system?

- ☐ Yes
- ☐ No
- ☐ Unsure

USEFULNESS

This section aims to determine how helpful the notification system is to public health staff.

Question 6. Who are the main users of varicella notification data?

- ☐ Jurisdictional Surveillance Officers
- ☐ Jurisdictional Immunisation Coordinators
- ☐ Commonwealth Surveillance staff
- ☐ Commonwealth Immunisation staff
- ☐ Researchers
- ☐ Other

If other (please specify)

Question 7. What are the uses of notification data, nationally?

Question 8. Has national notification system for varicella led to public health action in the following?

| | Yes | No | Unsure |
|----------|-----|----|--------|
| National | | | |

Question 9. Please provide details (if relevant).

Question 10. Has the national notification system for varicella led to changes in public health policy in the following?

| | Yes | No | Unsure |
|----------|-----|----|--------|
| National | | | |

Question 11. Please provide details (if relevant).

Question 12. To your knowledge, has varicella notifications led to the generation of national reports?

☐ Yes

☐ No

☐ Unsure

Question 13. Please provide details.

ACCEPTABILITY

The aim of this section is to measure how willing you are to participate in the current notification system.

Question 13. In your view, please rate the public health importance of varicella

- ☐ Extremely important
- ☐ Important
- ☐ Neutral
- ☐ Unimportant
- ☐ Extremely unimportant

Question 14. Do you think notifying varicella is a good use of you time?

- ☐ Yes
- ☐ No
- ☐ Unsure

Question 15. Please provide details (if any).

Question 16. Do you think the current requirements for varicella (chickenpox) case reporting in States and Territories is adequate?

- ☐ Yes
- ☐ No
- ☐ Unsure

Question 17. Please provide details.

the

national varicella notification system?

SIMPLICITY

This section aims to ascertain the structure of the system and its ease of operation.

Question 19. How would you describe the flow of information to the Department of Health and Ageing.

Question 20. In your opinion, do you think it is easy to report notifications to the NNDSS? Please explain your answer.

FLEXIBILITY

Question 21. How flexible do you think the national notification system is to change (for example to detect outbreaks once varicella incidence becomes low)?

STABILITY

Question 22. Do you think the notification system is stable in the following areas?

| | Yes | No | Unsure |
|---------------------|-----|----|--------|
| Data transfer | | | |
| Back-up of data | | | |
| Storage of data | | | |
| Release of data | | | |
| Unscheduled outages | | | |
| Capacity to run | | | |

| | | | |
|-------------|--|--|--|
| efficiently | | | |
| Maintenance | | | |

This section seeks information on your views on the national notification system for varicella.

Question 23. In your opinion, what are the strengths of the national system for varicella, for Australia overall?

Question 24. In your opinion, what are the limitations of the national notifications system for varicella, for Australia overall?

Question 25. In your opinion, how could the national varicella notification system be improved, for Australia overall?

Question 26. Further comments.

Thank you for completing the questionnaire

E5.1 Detailed case definitions of data sources used

APSU/PAEDS⁷²

| Disease | Case definition |
|---|--|
| Congenital Varicella | <p>Any stillbirth, newborn infant, or child <2 years who, in the opinion of the notifying paediatrician has definite or suspected congenital varicella syndrome, with or without defects and meets at least one of the following criteria:</p> <ul style="list-style-type: none"> • Cicatricial skin lesions in a dermatomal distribution and/or pox like scars and/or limb hypoplasia • Development of herpes zoster in the first year of life • Spontaneous abortion, termination, stillbirth or early death following varicella infection during pregnancy |
| Neonatal Varicella | <p>Any infant who, in the opinion of the notifying paediatrician, has neonatal varicella based on history (maternal varicella infection in the last 1-4 weeks of pregnancy of contact with a varicella infected person after birth), clinical and/or laboratory findings in the first month of life without features of congenital varicella syndrome. Features include:</p> <ul style="list-style-type: none"> • Pox-like rash which may be papulovesicular, vesiculopustular or haemorrhagic and fever. • Systemic symptoms may be present. <p>Confirmation of diagnosis:</p> <ul style="list-style-type: none"> • Viral antigen/viral isolate from scrapings of the skin lesions or viral DNA from lesion fluid. • Varicella specific IgM in a serum sample from the neonate or contact |
| Severe complications of varicella infection | <p>Any child aged 1 month – <15 years, hospitalised with varicella and one or more of the following complications:</p> <ul style="list-style-type: none"> • Bacteraemia/septic shock • Toxic shock syndrome/ toxin mediated disease • Septic arthritis or other focal purulent collections • Necrotising fasciitis • Encephalitis • Purpura fulminans/disseminated coagulopathy • X-Ray evidence of pneumonia • Fulminant varicella (multi-organ involvement) • Reye's syndrome • Ataxia |

Emergency Department visits (personal communication: Sophie Norton)

| Disease | Cases |
|------------|---|
| Chickenpox | <p>Keywords for chickenpox in diagnoses are coded based on the Australian edition of the International Classification of Diseases, version 9 and version 10, Clinical Modification (ICD-9-CM and ICD-10-CM) and the Systemized Nomenclature of Medicine Clinical Terminology (SNOMED CT). These classification systems were used in during different periods in different hospitals. A chickenpox presentation was recorded if it was the first provisional ED diagnosis.</p> |
| Shingles | <p>Keywords for shingles in diagnoses are coded based on the Australian edition of the International Classification of Diseases, version 9 and version 10, Clinical Modification (ICD-9-CM and ICD-10-CM) and the</p> |

Systemized Nomenclature of Medicine Clinical Terminology (SNOMED CT). These classification systems were used in during different periods in different hospitals. A chickenpox or shingles presentation was recorded if it was the first provisional ED diagnosis.

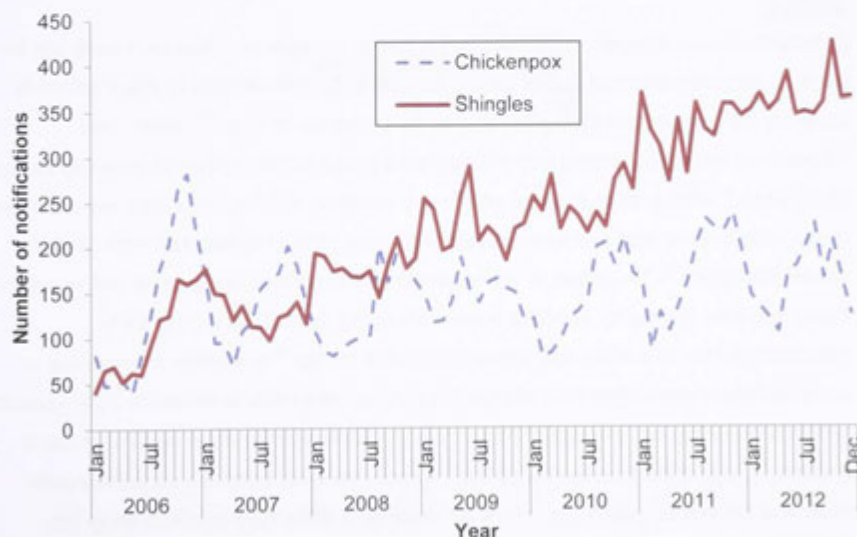
BEACH⁵¹

| Disease | Cases |
|------------|---|
| Chickenpox | International Classification of Primary Care, version 2(ICPC-2) code A72. |
| Shingles | International Classification of Primary Care, version 2(ICPC-2) code S70. |

E6.1 Notifications of chickenpox and shingles, Australia, 2006–2012^{*^}

NNDSSVZV notifications for chickenpox by month identified that peaks occurred during springtime (September/October). During 2009, a peak was also observed in April. As peaks in notifications did not occur in January to March, it was concluded that the BEACH March to April year could be compared to the calendar year (which is what is used for NNDSS data).

Figure E6.1 Notifications of chickenpox and shingles, Australia, 2006–2012^{*^}



* Since 2002, VZV infection became notifiable in South Australia

[^] Victorian data available 2009–2012, all other jurisdictions data available from 2006 except NSW where VZV is not notifiable

E7.1 Sensitivity and Specificity of tests used to diagnose varicella zoster virus infection

IF

Virus antigen detection by IF is a rapid (~ 2 hours)⁶⁷ and simple test method that can be used for early diagnosis. The test is highly sensitive (97–98%) and highly specific (100% when clinical diagnosis is considered the gold standard).⁶³

Virus culture

Viral isolation through cell culture is a diagnostic test for varicella zoster however can be difficult and slow. Test sensitivity is 49.4– 65% but is also dependent on the speed of processing following specimen collection.⁶³ Additionally, the sensitivity of cell culture is affected by how old the lesion is from where the specimen was taken as well as anti-viral treatment in an individual. Suspected varicella zoster isolates can be confirmed with direct IF.

Serology

Detection of virus-specific antibodies using paired acute or convalescent sera can be used to diagnose varicella zoster infection. However, the reliability of this method is lower for varicella zoster (shingles) due to the presence of specific antibodies.

⁶³Specimen collection should occur as soon as possible following rash onset to capture rising titres.⁶³ Within days of onset of primary infection, VZV-specific IgM are produced in the body but are also produced in approximately 70% of individuals with varicella zoster (shingles).⁶² Detection of VZV-specific IgM in serum suggests recent infection.⁶³ False negative results for varicella zoster (shingles) may occur during early presentation due to waning IgG below detectable levels.⁶⁷ A number of sensitive enzyme-linked immunosorbent assays (ELISA) are available to measure VZV –specific antibody including enzyme immunoassay (EIA), latex agglutination and fluorescent antibody to membrane antigen (FAMA).⁶³ Cross-reactivity between varicella zoster virus and herpes simplex virus can occur leading to difficulties in interpreting test results.⁶³

Chapter 6

Teaching

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Prologue

My role and lessons learned

During the MAE, I was given a number of opportunities to teach. This included Lessons From the Field (LFF), a 3.5 hour Introductory to Epi Info™ version 7 workshop conducted by the MAE 2012 cohort and providing teaching support during the 2013 outbreak investigation course.

My LFF was on measles elimination, a subject that I have had the opportunity to be involved in, through participating in the Measles Elimination Working Group. Using a framework of measles elimination criteria, I initially thought that it would be worthwhile for my colleagues to assess the elimination status of Australia. However, it became quite clear early on, that this could not occur as it would involve accessing a lot of sensitive data that at the time was being compiled, analysed and interpreted by the Measles Elimination Working Group. Instead, I provided data from a hypothetical country, with the main objective for my colleagues to follow the framework, and based on the compiled evidence, assess whether measles has been eliminated in the country.

LFF was a really enjoyable component of the MAE, both as a teacher and a student. Developing the LFF student guide was a new experience for me and I found it quite challenging to create a lesson from scratch, however, I feel that I learnt a great deal from it.

Following initial review by Steph, I learnt that the learning objectives that I had listed were not assessable. For example, one objective was 'to learn' which is not measurable. Also, I also learnt that my first LFF draft was too time consuming and that all activities in the LFF should always go back to the learning objectives. If they were not meeting these objectives, it was unnecessary to include them as a question or task.

Another important lesson learnt was that I needed to be more to be more careful in defining terms such as what a 'locally acquired' case was. I realised this, after receiving responses from my MAE cohort. A number of them had interpreted this to mean acquiring an endemic strain of measles virus. This ultimately impacted on the conclusions of whether measles had been eliminated and thus resulted in conflicting responses to what I originally had formulated.

The Epi Info™ version 7 teaching session admittedly was quite a daunting experience. Many of the participants were MAE alumni and well known public health experts. I was responsible for teaching on questionnaire development. This required preparing the student handout and facilitating this session during the workshop (including developing a power point presentation). I also had to be familiar with the content from the other sessions in the workshop to assist my fellow MAE colleagues. My only experience using Epi Info™ version 7 had been during the previous year's outbreak investigation course. The requirement to teach others something I had limited experience in, resulted in me spending time to ensure I understood the functions of Epi Info™ version 7. It was also a good opportunity to review my teaching style and communication techniques. One important lesson I learnt was that I needed to engage more with participants during my session, rather than directing them what to do and telling them the answers. I also learnt that it can be challenging to clearly explain concepts to others, even when you feel confident in your own knowledge. I hope this will improve with more experience teaching others. Ranil kindly nominated to draft an evaluation questionnaire for the workshop which is included in the Appendix.

Lastly, during two sessions in the outbreak investigation intensive course, I assisted the course convenor with two case studies. One involved facilitating a case study on arboviruses, whilst another was an introduction to Epi Info™. In reflection, this was a great opportunity to review my own development over the past year, from being a student in this course, to the following year, assisting in the teaching. Similar to the Epi Info session, I found it a good opportunity to try to explain concepts to others in a concise manner. Another important lesson I learnt was that teaching is not easy. We have been fortunate to have such incredible teachers during our MAE who make it look effortless, and these teaching experiences made me realise that a lot of hard work and planning goes into preparing and facilitating lessons.

Acknowledgements

I would like to thank my MAE cohort for their patience, encouragement and teamwork during these teaching experiences. If ever in doubt, my MAE colleagues would always be at hand to support me during the teaching sessions, and often as a team we would work out a solution.

Additionally, thank you to Stephanie Davis, Martyn Kirk and Bridget O'Connor who attended the Epi Info™ workshop and provided support and constructive feedback. I'd

also like to acknowledge Stephanie for the time she spent reviewing my LFF and the feedback she provided.

Abbreviations and Acronyms

| | |
|-------|--|
| ANU | Australian National University |
| ID | Infectious Disease |
| IF | Immunofluorescence |
| IgG | Immunoglobulin G |
| IgM | Immunoglobulin M |
| MAE | Master of Applied Epidemiology |
| MCV | Measles Containing Vaccine |
| MCV1 | Measles Containing Vaccine– Primary Dose |
| MCV2 | Measles Containing Vaccine– Booster Dose |
| NCIRS | National Centre for Immunisation Research and Surveillance |
| PCR | Polymerase Chain Reaction |
| WHO | World Health Organization |
| WPRO | Western Pacific Regional Office |

Appendix F

F1. Lessons from the field– Student guide with answers

Lessons From the Field

The Verification of Measles Elimination in the Western Pacific: Has Country X achieved elimination?



May Chiew

Master of Philosophy Applied Epidemiology (MAE) Scholar

Australian National University (ANU) &

National Centre for Immunisation Research & Surveillance (NCIRS)

10 June 2013

The learning objectives for this Lesson From the Field are that by the end of this session participants will be able to:

- describe the difference between disease elimination and disease eradication;
- discuss the framework for the verification of measles elimination;
- calculate a measles discard rate;
- estimate R using proportion of imported cases;
- assess the evidence provided using the framework for verification and consider elimination in the context of Country X;
- determine the feasibility of the framework in a low-resource setting and consider barriers that may impede measles elimination;
- list of the characteristics of measles that makes eradication biologically and technically feasible.

Readings:

1. World Health Organization (2013). "Framework for verifying elimination of measles and rubella." *Weekly epidemiological record* **9**(88): 89-100.
 2. De Serres, G., Gay N. J., et al. (2000). "Epidemiology of transmissible diseases after elimination." *American Journal of Epidemiology* **151**(11): 1039-1048.
- (Optional)

Part 1: Case Study Introduction

Following the completion of your MAE, you have moved to the small idyllic island of Country X in the Western Pacific Region to be their newly employed Infectious Disease (ID) Epidemiologist.

Your Director informs you that one of your first roles as the only ID Epidemiologist on the island is to gather all the evidence for the Regional Measles Verification Committee to assess whether measles elimination has been achieved in Country X. She informs you that this work is important, as 2012 was the set target year for elimination and all Member States are required to submit the evidence to Western Pacific Regional Office (WPRO) by the end of the year.

Unsure of where to start, she hands you a copy of the March edition of the Weekly Epidemiological Record (Reference 1) and recommends that you read the article 'Framework for verifying the elimination of measles and rubella' and follow the framework as a guide to assess the elimination status of Country X. Before you start you would like to refresh what disease elimination and disease eradication are.

Question 1. Please define disease elimination and eradication and explain the difference between the two. (5 minutes)

Ee Laine

Eradication = Worldwide interruption of disease transmission with permanent reduction to zero incidence of infection as a result of deliberate efforts

Elimination = The absence of endemic transmission in a defined geographical area (e.g. region or country) for ≥ 12 months as a result of deliberate efforts.

Continued intervention measures required for disease elimination, but not for necessarily eradication (although ongoing surveillance may be required. Zero incidence of disease in eradication, but not in elimination as there may be sporadic cases with no evidence of transmission.

You decide to go through the Framework systematically and consider the 5 lines of evidence for the verification of measles elimination:

1. A detailed description of the epidemiology of measles since the introduction of measles in the national immunisation program
2. Quality of epidemiological and laboratory surveillance systems for measles
3. Population immunity presented as a birth cohort analysis with the addition of evidence related to an underserved and marginalised groups
4. Sustainability of national immunisation programmes, including the resources for mass campaigns, where appropriate, in order to sustain measles elimination
5. Genotyping evidence that supports measles virus transmission is interrupted

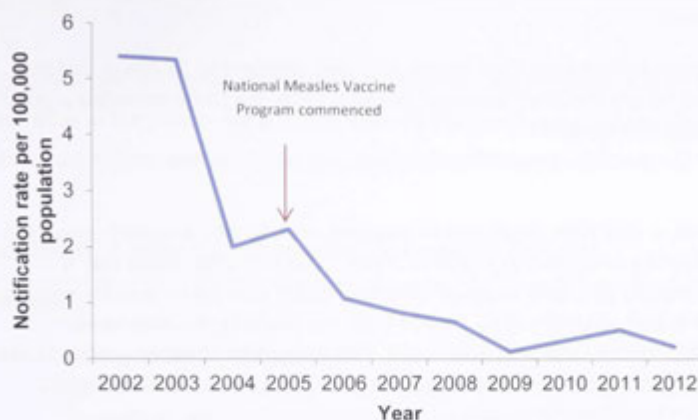
In Country X, a national measles vaccination program was rolled out in 2004, where a two-dose schedule was funded for children 12 months old (primary dose) and 4 years old (booster dose).

The case definition of a confirmed case of measles in Country X is an individual with laboratory confirmation of measles by: Positive serological test for measles IgM antibody or; Isolation of measles virus or; Detection of measles-virus nucleic acid by polymerase chain reaction (PCR) or; A fourfold or greater rise in measles antibody level or IgG seroconversion (except if the individual had received a measles containing vaccine eight days to eight weeks before testing). A confirmed case could also be an individual with clinical evidence of disease including: a generalised rash lasting ≥ 3 days and; temperature 38°C and; cough, coryza, or conjunctivitis; and an epidemiologic linkage to a confirmed case of measles.

Line of Evidence 1. A detailed description of the epidemiology of measles since the introduction of measles in the national immunisation program

Fortunately, the previous ID epidemiologist conducted descriptive analysis on confirmed measles cases in Country X in 2002-2012 and has left the output for you to use.

Graph 1- Notification rate of confirmed measles cases, 2002–2012 Country X

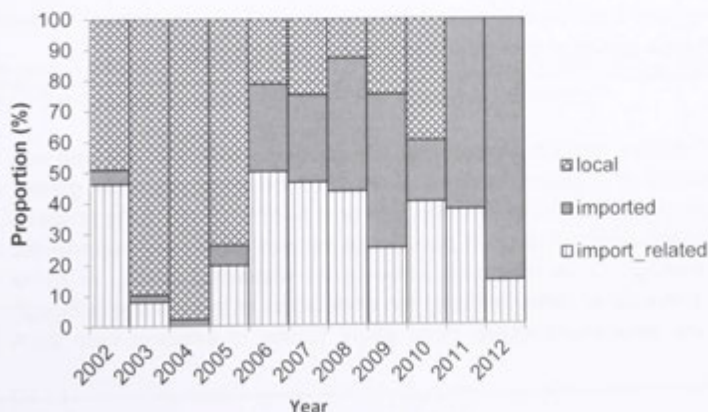


Question 2. Please interpret Graph 1. (5 minutes)

Alexis

Between 2002-2004 there was a decrease in confirmed measles notifications from $>5/100,000$ to $\sim 2/100,000$. Following the introduction of the national vaccination program in 2004, rates decreased progressively from $\sim 2/100,000$ in 2009. There has been a slight increase in notifications since the low in 2009.

Graph 2- Proportion of cases with a known source of infection by importation status



Question 3. Please interpret Graph 2. (5 minutes)

My comments:

I should have defined what local meant as it was interpreted by many that this meant endemically acquired measles. Based on this, Ee Laine provided a good interpretation of the graph.

Ee Laine

Before 2006, a very high proportion of measles were locally acquired (except in 2002), indicating endemic transmission. From 2006 onwards, there was a continued decline of locally acquired measles, which was taken over by imported cases and import_related cases. By 2011-12, the majority of cases were imported with zero locally acquired cases. The proportion of import_related cases has declined from 2006 onwards, suggesting a decline in the chain of local transmission from imported cases.

Table 1. The proportion of cases by known source of infection by year, Country X, 2002-2012

| | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 |
|--------------------|------|------|------|------|------|------|------|------|------|------|------|
| Known source (%) | 70.3 | 47.3 | 63.4 | 55.4 | 71.8 | 93.3 | 95.8 | 80.0 | 83.3 | 84.2 | 87.5 |
| Unknown source (%) | 29.7 | 52.7 | 36.6 | 44.6 | 28.2 | 6.7 | 4.2 | 20.0 | 16.7 | 15.8 | 12.5 |

Question 4. Please interpret the results in Table 1. (5 minutes)

Rowena

Prior to 2007 there is less information available about the source of infection with between 28–53% of sources unknown. From 2007 onwards, we have greater information regarding source of infection with only 4–17% of infections acquired from an unknown source. This could possibly be the product of rarer occurrences of measles making it more realistic to follow up all suspected cases, or better surveillance follow up of cases following the introduction of the vaccine (although if this was the case you'd expect more about source of infection from 2004 onwards).

Line of Evidence 2. Quality of epidemiological and laboratory surveillance systems for measles

Country X has a central laboratory which tests for measles. It is conveniently located next door to the health department. You organise a meeting with the virologist at the laboratory so you can ascertain the quality of laboratory surveillance in Country X.

Questions: 5 What questions would you ask? (5 minutes)

Rowena

- Is the lab WHO accredited?
- Which measles testing they do (i.e. PCR, serology and/or IF) and the sensitivity and specificity of these tests
- What is the turnaround time to perform the tests and inform public health of positive result?
- Are they able to perform measles genotyping?
- Number of measles tests performed including positive and negative specimens
- Where are they receiving specimens from (e.g. is it only hospitals or are GP's testing too?)

The virologist is very forthcoming with answering all your questions.

The laboratory is WHO accredited for serological and virological measles tests and services the entire country. Quality assurance mechanisms are in place at the laboratory for measles testing and occur annually. Approximate 82% of serological results are reported to the laboratory within 4 days of receiving the specimen.

He also provides you a table of IgM, PCR and IF tests conducted between 2007 and 2012 (by test type) and the number of tests that were positive.

Table 2. Number of positive and total tests by test type and year (2007 between 2007–2012)

| Test type | Year | | | | | | | | | | | |
|-----------|----------|-------------|----------|-------------|----------|-------------|----------|-------------|----------|-------------|----------|-------------|
| | 2007 | | 2008 | | 2009 | | 2010 | | 2011 | | 2012 | |
| | Positive | Total tests | Positive | Total tests | Positive | Total tests | Positive | Total tests | Positive | Total tests | Positive | Total tests |
| IgM | 5 | 13 | 3 | 6 | 1 | 3 | 1 | 8 | 2 | 11 | 1 | 11 |
| PCR | 20 | 121 | 12 | 89 | 3 | 100 | 8 | 120 | 11 | 120 | 5 | 79 |
| IF | 5 | 16 | 9 | 40 | 1 | 20 | 3 | 20 | 6 | 20 | 2 | 16 |
| Total | 30 | 150 | 24 | 135 | 5 | 123 | 12 | 148 | 19 | 151 | 8 | 106 |

$$\text{The reporting rate of non-measles cases (discard rate)} = \frac{\text{No. negative tests}}{\text{Population estimate}} \times 100,000$$

He also answers all your questions:

Question 6. Calculate the national measles discard rate for the combined years 2007–2012. (5 minutes)

Ee Laine

Total tests = $150+135+123+148+151+106 = 813$

Total positive tests = $30+24+5+12+19+8 = 98$

Total negative tests = $813-98 = 715$

Total population estimate (2007-2012) = 21641298

Discard rate = $715 / 21641298 \times 100,000 = 3.3 \text{ per } 100,000$

Question 7. How might sensitivity and specificity of tests impact on the result?

Are there any other biases you can think of? (5 minutes)

My comments

Rowena had an excellent response but did not mention the possible biases. Ee Laine pointed out some important biases including the selective testing of cases with suspected illness. If testings are only performed on cases with a high index of suspicion, this could result in a higher proportion of positive tests. Conversely, if testing is done indiscriminately, this may result in a higher proportion of negative tests. Additionally, I had in my answer that screening of individuals for measles immunity could overestimate the discard rate, if included in this analysis.

Rowena

A high sensitivity will increase the probability that the test results will be positive in people who truly have measles. (i.e. high proportion of true positive results). Conversely a test that has lower sensitivity will be more likely to give more falsely negative results, falsely labelling people with measles as non-measles cases and underestimating cases numbers.

High specificity will correctly return negative test results in people who don't have measles (i.e. High proportion of true negatives). Lower specificity will give more false positives (i.e a high proportion of people who don't have measles will have lab results indicating they do have measles, thus overestimating measles case notifications).

To find out more about the quality of epidemiological surveillance in Country X, you go through a number of annual reports back at the office. You discover that since 2000, the investigation of suspected cases of measles and specimens were taken for 81% of all suspected cases. Upon looking at your data, you also find that at least one confirmed case for every identified outbreak had a specimen that was genotyped.

Question 8. Based on the evidence you collected about laboratory and epidemiologic surveillance, can you conclude that they are of high quality in Country X? (2 minutes)

Ee Laine

The data reviewed fulfilled the targets outlined in the indicators for quality of lab reporting:

- Discard rate is within the target of ≥ 2 cases per 100,000
- Results reported within 4 days of specimen receipt
- Over 80% of suspected cases investigated and specimens collected (although it is not clear if adequate specimen was taken).

Furthermore, genotyping information was obtained for at least one confirmed case for every identified outbreak. There were also continued improvements in information on source of infection.

To determine the coverage of measles containing vaccine (MCV– primary (MCV1) and booster dose (MCV2)), you access the childhood immunisation register. The register is estimated to capture 98% of all children under the age of 8 in Country X. You analyse two birth cohorts, children aged 2 years (MCV1– to measure the primary dose of measles containing vaccine) and children aged 5 years (MCV2– to measure the booster dose of measles containing vaccine). Coverage of MCV1 was 92% and MCV2 89% and based on geography, there was little heterogeneity in coverage around the country.

Question 9. Can you think of any reason that might lead to the underestimation of coverage rates? (5 minutes)

My comments

This question may have been difficult to answer without knowledge of the caveats to immunisation registry data, such as what is experienced in Australia.

My answer

It is possible that not all immunisations are recorded by the register and there is under-reporting of vaccination status. This was observed in Australia where the Australia Childhood Immunisation Register underestimated MCV1 by 3–5% and MCV2 by 5–10%. If this is the case in Country X, it is likely that the coverage rates of each birth cohort is high (i.e. > 95%).

Estimating an effective reproduction number using the proportion of imported cases

Complementary evidence of population immunity is the estimation of the reproduction number (R). R is the average number of secondary cases that results from an infectious case in a particular population. When $R = 1$, a state of endemic equilibrium exists where on average one case results in one secondary infection. When $R > 1$, the number of cases increases from one generation to the next, potentially resulting in an epidemic. In comparison, when R is maintained below 1, measles is considered to be eliminated.

One method to estimate R is through the proportion of imported cases (please note: the assumption of this method is that measles has already been eliminated – for more information on the theory of this method, please refer to Reading 2)

$$R = 1 - \frac{\text{No. of imported cases}}{\text{Total no. of cases}}$$

Question 10. Based on the proportion of imported cases (below), estimate the reproduction number for individual years 2009–2012 and also the combined estimate of R for these years. Please interpret your results. (10 minutes)

| Import status | 2009 | 2010 | 2011 | 2012 |
|----------------|------|------|------|------|
| Imported cases | 2 | 2 | 10 | 6 |
| Total | 5 | 10 | 16 | 7 |

Alexis

2009: $R = 1 - 2/5 = 0.6$

2010: $R = 1 - 2/10 = 0.8$

2011: $R = 1 - 10/16 = 0.375$

2012: $R = 1 - 6/7 = 0.143$

Total: $R = 1 - 20/38 = 0.474$

R is the average number of secondary cases resulting from an infectious source case. With an R less than 1, as these results all are, measles is considered to be eliminated.

Question 11. Based on the lines of evidence, is there strong evidence that population immunity is high? What other measures of population immunity exist? (5 minutes)

Ee Laine

Based on the vaccine coverage (assuming an under-estimation) and declining R , there is some evidence that population immunity is high. However further evidence will be needed – for e.g. vaccine coverage in sub-population groups (children, adolescents), vaccine effectiveness, outbreak duration, number of generations of measles transmission and proportion of import-related cases.

Other measures of population immunity are seroprevalence surveys, supplementary immunisation activities, and those described above.

Line of Evidence 4. Sustainability of national immunisation programmes, including the resources for mass campaigns, where appropriate, in order to sustain measles elimination

To determine how sustainable the current measles vaccination program and political commitment for measles elimination, you review a number of plans and reports in the office in relation to measles. This includes the bi-annual monitoring of the vaccination program, a proposal for the evaluation of the program in the coming year, an action plan for the financing and sustaining measles elimination and a risk assessment on the program.

Question 12. Are there any other documents that you think may assist in enhancing the evidence? (2 minutes)

Rowena

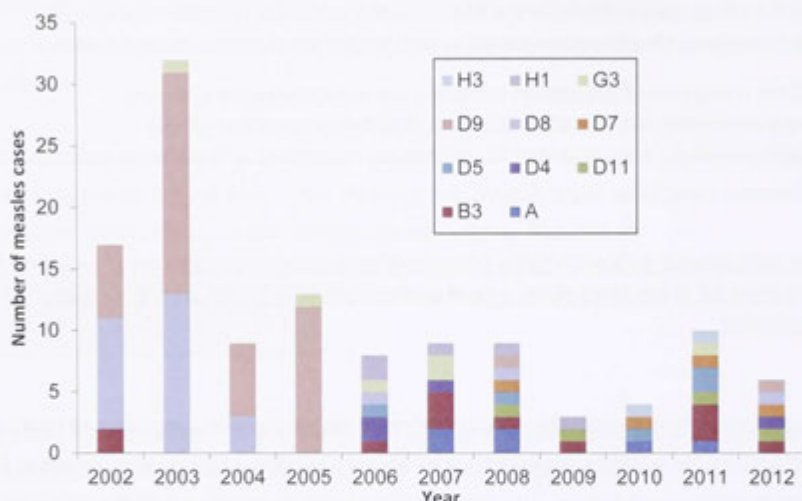
Some of these documents may already be included as part of the bi-annual monitoring of the vaccine program & action plan but we'd want to make sure that the following are included:

- Country X's budget showing ongoing item(s) dedicated to vaccination
- Vaccine demand forecasting and stock management
- Tools assisting standardised program implementation – i.e. guidelines/checklists for mass vaccine administration such as in school settings.

Line of Evidence 5. Genotyping evidence that supports measles virus transmission is interrupted

The previous ID epidemiologist has also produced output on measles genotypes over the past decade.

Graph 3 Number of cases by genotype in Country X, 2002–2012



Question 13. Please interpret Graph 3 with reference to the Framework (5 minutes)

Alexis

There was a lot of D8 and D9 in 2002-2005. These were most likely the locally circulating strains. Following the introduction of the vaccination program, this has changed, and from 2005 the combination of strains each year is quite varied suggesting that endemically circulating strains have been replaced by imported ones.

Question 14. After applying the framework for measles elimination and reviewing the evidence, do you think that measles has been eliminated from Country X? Please give your reasons. (5 minutes)

My comments

I received conflicting answers for this question with one colleague concluding that despite not having information on a number of indicators, based on what was provided measles can be considered eliminated. I think it reflects the difficulty in assessing elimination verifications as all countries have different systems and in some way, indicators in this framework may not be able to fit with each countries capacity.

Ee Laine

Looking at the essential verification criteria, I think that measles elimination has not been achieved in Country X

- Documentation of the interruption of endemic measles transmission for a period of at least 36 months from the last known endemic
 - Criteria not met as there were only two years of absent locally acquired measles.
 - Furthermore, for import_related cases, we need to know if transmission occurred for how many generations after importation – at what point do we define this as sustained transmission that occurred locally?
- the presence of a high-quality surveillance system that is sensitive and specific enough to detect imported and import-related cases;
 - Criteria met as there is some evidence of high quality of epidemiological evidence (over 80% of source known, over 80% of suspected cases investigated and specimens collected)
- Genotyping evidence that supports the interruption of endemic transmission
 - Criteria not met if the circulating endemic strains (D8 and D9) are not found elsewhere in the world.
- Population immunity presented as a birth cohort analysis with the addition of evidence related to any marginalised and migrant groups
 - I think we need vaccine coverage of 95% for measles, so the current coverage remains inadequate. Also we do not have sufficient information on coverage in specific populations

Question 15. As measles elimination becomes a priority in less developed countries, how feasible do you think these guidelines are in low resource settings? (5 minutes)

Rowena

For countries getting close to elimination:

- Groups of susceptible people who live in close proximity (e.g. geographical areas of conscientious objectors, non-immune immigrant communities)
- Delay in diagnosis of measles (particular as it becomes rarer and health providers no longer recognise symptoms) thus decreasing the ability of public health authorities to isolate, vaccinate or administer immunoglobulin to prevent further cases.
- Increased international travel, increasing cases being imported
- Ability of the virus to infect susceptible hosts (?up to 4 hours after leaving a room!)

For developing countries;

- Lack of resources including money to fund sustainable vaccination program
- Conflicting priorities (e.g famine, war)
- Lack of infrastructure (e.g. to store vaccines, accredited labs to test)
- Lack of political willpower

Question 16. What do you think are the main barriers to achieving disease elimination in a country? (5 minutes)

Ee Laine

- Lack of political will, commitment and funding for immunisation program and vaccine procurement
- Lack of a clear national strategy to provide direction and coordinate interventions to support elimination
- Lack of collaboration and partnerships from different groups to implement the strategy
- Lack of adequate infrastructure including laboratory support and surveillance
- Lack of a mechanism for effective vaccine delivery
- Lack of demand or distrust from the general public wanting vaccination

Question 17. What are the properties that make the eradication of measles feasible? (5 minutes)

Ee Laine

Properties related to the disease

- Humans are the only hosts for the virus and the main mode of transmission (i.e. no environmental or animal reservoir)
- Diagnostic tools available
- Long lasting immunity resulting from infection or vaccination
- Presence of a highly effective vaccine

Properties related to social and political climate

- Strong political commitment to do so worldwide, including funding
- Global partnerships and coordination towards eradication

Evidence that it is possible to eliminate the disease in a large geographical area, therefore making it feasible to consider eradication

End of Lessons From the Field

Thanks for your time!

F2. Workshops for Communicable Disease Control Conference 2013

F2.1 Introduction to Epi Info™ Version 7

Summary of session outline

| Topic | Format | Time (pm) |
|--|---|-------------|
| Topic 1: Welcome and introduction <ul style="list-style-type: none"> • Introduction – staff and participants • Logistics | Round table | 1.30 – 1.40 |
| Topic 2: Introduction to Epi Info and the training session <ul style="list-style-type: none"> • Learning objectives • Epi Info <ul style="list-style-type: none"> ◦ Overview ◦ Capabilities and uses • Format of session | Power point presentation | 1.40 – 1.55 |
| Introduction to case study | Power point presentation | 1.55 – 2.00 |
| Topic 3: Questionnaire and maps <ul style="list-style-type: none"> • Learning objectives • Introduction to questionnaires and maps • Create form • Enter data • Create a cluster map | Power point presentation Instruction demonstration Participant activities | 2.00 – 3.00 |
| Break for 15 minutes | | |
| Topic 4: Overview of data analysis <ul style="list-style-type: none"> • Classic and visual dashboard | Power point presentation | 3.15 – 3.20 |
| Topic 5: Data analysis using visual dashboard <ul style="list-style-type: none"> • Learning objectives • Data import / export, open Epi Info dataset • Descriptive statistics <ul style="list-style-type: none"> ◦ Frequency tables, summary statistics • Recode variables • Create graphs / epi curve • 2x2 tables | Instruction demonstration Participant activities | 3.20 – 4.15 |
| Topic 6: Classic analysis | Instruction demonstration | 4.15 – 4.30 |
| Topic 7: Stat calc <ul style="list-style-type: none"> • Introduce the range of statistical functions and when to use them • Use stat calc to assess if ↑ cases occur by chance | Power point presentation Instruction demonstration Participant activities | 4.30 – 4.45 |
| Summing up discussions and final questions Evaluation forms | Instructor leads discussion | 4.45 – 5.00 |

F2.2 EpiInfo™ 7 workshop presentation

Australian National University

Topic 3

Questionnaires and Maps in Epi Info™

Instructors: Rowena Boyd and May Chiew

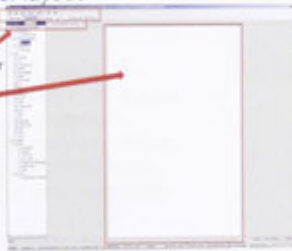
Australian National University

Objectives

- Create a new Project in Form Designer
- Create different field types using the Form Designer module
- Add intelligence into Forms
- Format a questionnaire
- Use templates in a questionnaire
- Enter data in different field types
- Create a cluster map based on information in a dataset

Australian National University

Form Designer layout



1. Menu and toolbar
2. The Project Explorer
3. The Canvas

Australian National University

Session Outline

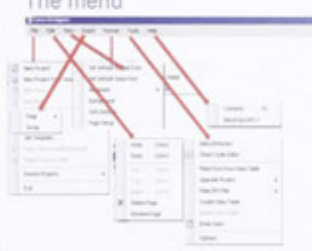
- Learning objectives
- Introduction to questionnaires and mapping
- Developing a questionnaire
 - creating a new Project
 - creating different field types
 - using the Check Code Editor
 - finalising and formatting
- Entering data into a questionnaire
- Creating a cluster map

Australian National University



Australian National University

The menu



Field types

| Question | Field name | Field Type | Categories/Patterns |
|---|---------------|----------------------|---------------------------------|
| Surname | surname | Text | |
| Age | age | Number | ### |
| Date of birth | dob | Date | DDMMYYYY |
| Sex | sex | Legal Values | Male Female Unknown |
| Sex | sex | Comment/legal values | 1-Male 2-Female 3-Unknown |
| Current smoker Past smoker Non smoker | smokingstatus | Checkbox | |
| Did you consume chicken? | chicken | Yes/No | Yes/No |

F2.3 Epi Info™ Version 7 Workshop Evaluation Questionnaire

This is a short evaluation of the Epi Info 7 course that was run on 18 March 2013. Thank you for taking the time to complete this form. The information will be used to improve future sessions.

1. How well organized was the Epi Info™ 7 course?

- ☐ Extremely organized
- ☐ Very organized
- ☐ Moderately organized
- ☐ Slightly organized
- ☐ Not at all organized

2. How useful to your job was the information presented at the Epi Info™ 7 course?

- ☐ Extremely useful
- ☐ Very useful
- ☐ Moderately useful
- ☐ Slightly useful
- ☐ Not at all useful
- ☐ Other (please specify) _____

3. How much have your skills improved because of training at the course?

- ☐ A great deal
- ☐ A lot
- ☐ A moderate amount
- ☐ A little
- ☐ None at all

4. How comfortable did you feel asking questions at the course?

- ☐ Extremely comfortable
- ☐ Very comfortable
- ☐ Moderately comfortable
- ☐ Slightly comfortable
- ☐ Not at all comfortable

5. How friendly were the presenters?

- ☐ Extremely friendly
- ☐ Very friendly
- ☐ Moderately friendly
- ☐ Slightly friendly
- ☐ Not at all friendly

6. Did the presenters allow enough time for the computer exercises?

- ☐ Much too much
- ☐ Somewhat too much
- ☐ Slightly too much
- ☐ About the right amount
- ☐ Slightly too little
- ☐ Somewhat too little
- ☐ Much too little

7. How easy was it to keep up with the exercises?

- ☐ Extremely easy
- ☐ Very easy
- ☐ Moderately easy
- ☐ Slightly easy
- ☐ Not at all easy

8. What suggestions do you have for improving this Epi Info™ course if it were to be run again?

9. Overall, how satisfied were you with the Epi Info 7 course?

- ☐ Extremely satisfied
- ☐ Moderately satisfied
- ☐ Slightly satisfied
- ☐ Neither satisfied or dissatisfied
- ☐ Slightly dissatisfied
- ☐ Moderately dissatisfied
- ☐ Extremely dissatisfied

10. If you have any comments about the Epi Info 7 course, please write them below:

THANK YOU FOR COMPLETING THIS EVALUATION!!

F2.4 Evaluation of the Introduction to Epi Info 7 workshop

At the completion of the Epi Info 7 teaching exercise, an evaluation form was handed out to all the participants. Ten responses were received. The responses to the questions in the evaluation forms appear below:

1. How well organized was the Epi Info 7 course?

Two of the ten participants (20%) stated it was "extremely organized", eight (80%) stated it was "very organized" and 1 participant (10%) stated it was "moderately organized".

2. Had you used Epi Info before this session (you can tick more than one box)?

Three participants (30%) answered "Yes - a bit", two participants (20%) answered "Yes - but a long time ago", 4 participants (40%) answered "no" and one participant (10%) answered "Yes – but a long time ago" and "Yes- but an older version"

3. How useful to your job was the information presented at the Epi Info 7 course?

Six participants (60%) answered that it was "very useful" and four participants (40%) answered that it was "moderately useful".

4. How much have your skills improved because of training at the course?

One participant (10%) answered " a great deal", four participants answered "a lot" and four participants (40%) answered a moderate amount. One participant did not answer the question.

5. How comfortable did you feel asking questions at the course?

Two participants (20%) answered "extremely comfortable" and eight participants (80%) answered "very comfortable".

6. How friendly were the presenters?

Five participants (50%) answered "extremely friendly" and five participants (50%) answered "very friendly"

7. *Did the presenters allow enough time for the computer exercise?*

Eight participants (80%) answered that it was "about the right amount", 1 participant (10%) answered that it was "slightly too little". One participant wrote: "varied sometimes too little, depended on program playing up"

8. *How easy was it to keep up with the exercise?*

Two participants (20%) answered that it was "extremely easy", four participants (40 %) answered that it was "very easy", and four participants (40%) answered that it was "moderately easy".

9. *What suggestions do you have for improving the Epi Info course if it were to be run again?*

Comments received were:

- "Larger screen, sometimes difficult to see what presenter was doing. If bringing laptop, more information on system requirements"
- "More exercises to work through"
- "Invite participants to bring current dataset under investigation"
- "Keep class size small"

10. Overall, how satisfied were you with the Epi Info 7 course?

Six participants (60%) answered that they were "extremely satisfied" and four participants (40%) answered that they were "moderately satisfied".

11. If you have any comments about the Epi Info 7 course, please write them below:

Comments received were:

- "Thank you...now I'll know where to start when that outbreak hits!!"
- "Good course materials"
- "Thanks for allowing this great opportunity. Cheers"